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Announcement

CHRONIC FUNGUS INFECTIONS SYMPOSIUM

A Symposium on Chronic Fungus Infections, with Dr. David T. Smith, Professor of Medicine, Duke University, as Guest Editor, will appear in the April issue of the JOURNAL. The Symposium will include the following titles and authors:

1. *Actinomycosis and Nocardiosis:* J. Winthrop Peabody, M.D., Washington, D. C., and John H. Seabury, M.D., New Orleans, La.
2. *North American Blastomycosis:* Arthur C. Curtis, M.D., and Florante C. Bocobo, M.D., Ann Arbor, Mich.
3. *Coccidioidomycosis:* William A. Winn, M.D., Springville, Calif.
4. *Cryptococcosis (Torulosis, European Blastomycosis, Busse-Buschke's Disease):* J. Walter Wilson, M.D., Los Angeles, Calif.
5. *Species of Candida Most Frequently Isolated From Man: Methods and Criteria for Their Identification:* Rhoda W. Benham, Ph.D., New York, N. Y.
6. *Histoplasmosis:* Clayton G. Loosli, Ph.D., M.D., Chicago, Ill.
7. *Epidemic Histoplasmosis:* Patrick H. Lehan, M.D., and Michael L. Furcolow, M.D., Kansas City, Kan.
8. *Fungus Infections of the Hair and Nails:* Norman F. Conant, Ph.D., Durham, N. C.
9. *Superficial Mycotic Infections of the Skin: Diagnosis and Therapy:* J. Lamar Callaway, M.D., and Sidney Olansky, M.D., Durham, N. C.
10. *Miscellaneous Fungus Diseases:* David T. Smith, M.D., Durham, N. C.
11. *Cultural Methods for Human Pathogenic Fungi:* Libero Ajello, Ph.D., Chamblee, Ga.
12. *The Diagnosis of Fungus Diseases by Biopsy:* Roger Denio Baker, M.D., Durham, N. C.
13. *Serologic Reactions in Coccidioidomycosis:* Charles E. Smith, M.D., and Margaret T. Saito, B.S., Berkeley, Calif.
14. *Evaluation of Skin Tests and Serologic Methods in Fungus Infections:* Donald S. Martin, M.D., DPH, Atlanta, Ga.

Original Communications

STUDIES IN HYPERTENSION

V. Psychologic Factors in Hypertension: An Interpretative Review

Charles Y. Glock, Ph.D., and Henry L. Lennard, Ph.D.

New York, N. Y.

(Received for publication May 5, 1956.)

From the Division of Epidemiology, School of Public Health and Administrative Medicine of the Faculty of Medicine and the Bureau of Applied Social Research, Columbia University

THIS paper, the fifth in the series reporting on certain aspects of the Columbia University hypertension project, deals with the role of psychologic factors in hypertension. Its objectives are these: one, systematically to review and evaluate current hypotheses bearing on the association between psychologic variables and the onset and presence of hypertension; and two, to consider how, if at all, these hypotheses might be fruitfully subjected to further examination in a long-term epidemiologic study of hypertension.[27] The discussion which follows considers both the presently postulated associations between psychologic factors and hypertension and the manner of the associations.

PSYCHOLOGIC FACTORS POSTULATED AS ASSOCIATED WITH HYPERTENSION

It is suggested that the variety of extant hypotheses on this topic can be ordered, for heuristic purposes, into three broad classifications: those emphasizing the whole configuration of characteristics making up the so-called hypertensive personality; those considering specific psychologic conflicts as the unit of psychologic description; and those dealing with conditions of psychologic stress.

1. The "Hypertensive Personality."—A number of investigators, among them Palmer,[1] Tucker,[2] Ayman,[3] Dunbar,[4,5] and Gressel and his associates[6] have postulated the idea of a hypertensive personality, i.e., a set of psychologic characteristics which in combination are related to the occurrence of hypertension.

Palmer describes the "hypertensive personality" as "ambitious, energetic, often mercurial, with alternations of mood seemingly with or without relation to life situation or actual achievement." He further states that the majority

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of his cases "appeared to be extroverted in attitude, varying from a cheerful and even elated mood to dejection, soft heartedness, sentimentality, or mild depression but usually without abnormally wide swings. On the whole they were smart and enterprising, often habitually talkative, gesturing freely, adjusting well in ordinary social intercourse, were generally of the practical and realistic sort."

Tucker describes the characteristic configuration as follows: "conscientiousness, strong devotion to duty, a reputation for scrupulous honesty, perfectionistic and meticulous, have high ideals but are never satisfied with their work. They value independence and try to avoid dependence on others but are often highly sensitive to criticism and apt to be crushed by failure."

Ayman concludes that hypertensives "tend to be highstrung individuals who either display quick temper or are easily excited within themselves, tend to be unusually sensitive, being hurt by little things. In youth and often persisting into later life, they tend to blush easily, to be easily embarrassed and to be unusually shy. In dealing with events of life, however minute, they tend to be unusually serious and worry about trivialities."

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Dunbar also offers a set of hypotheses delineating the hypertensive profile. She attributes these behavior patterns to the hypertensive individual: "shyness in social relationships, fearfulness of not making the grade, use of wine, women and song to compensate, secret but compulsive promiscuity, yet insecurity and frequent impotence or frigidity, excessive use of coffee, cigarettes and alcohol, tendency to seek satisfaction within oneself, devotion to long-range goals. In the attitudes toward their own family, there is an alleged show of ambivalence toward father, though hostile and fearful of mother."

Gressel and his group offer the view that a tendency to "obsessive-compulsive behavior and subnormal assertiveness differentiate significantly hypertensives from those having personality disorders without hypertension."[6] They further state that patterns of hysteria, anxiety, depression, and subnormal assertiveness differentiate hypertensive individuals from those suffering from chronic somatic disorders.

The foregoing are representative of the statements found in the literature on the psychologic characteristics of the so-called "hypertensive personality." The utility of this concept might be viewed in terms either of its contribution to an understanding of the hypertensive disorder or its suitability as a point of departure for further research. It is doubtful, however, that the hypothesis can serve either of these functions at its present stage of development. Some of the difficulties are given in the following paragraphs.

a. *The formulations of the hypothesis by different investigators are neither consistent nor theoretically integrated:* Comparing the descriptions advanced by the investigators cited above, there are striking dissimilarities in the number and content of the traits singled out as significant. Palmer's description,[1] for example, emphasizes the "affective" dimension. Tucker[2] mentions characteristics usually referred to as "traits of character." Gressel and his co-workers[6] are, surprisingly, the only investigators who adopt traditional psychologic terminology in their descriptions. Though the dissimilarities are many and

obvious, this is not to say that the descriptions are highly contradictory. In several instances, however, some apparent contradictions are to be noted. For example, Palmer's assertion that the hypertensive is extrovert in attitude does not seem to coincide with Ayman's description of him as shy. In general, however, the dissimilarities derive not so much from the contradictions as from differences in the kind of characteristics considered.

This difficulty is explained, in part, perhaps by the fact that the investigators have not considered it their function to integrate their observations theoretically. There is no indication made, for example, as to the theoretical reasons why particular characteristics might be expected to appear jointly. Furthermore, the investigators are not explicit as to what led them to consider certain traits and not others. Thus it cannot be determined to what extent the descriptions are considered complete or exhaustive.

b. *The evidence offered in support of the hypothesis is limited:* Generally speaking, most of the personality descriptions under discussion are based on observations made by the investigators on hypertensive subjects. The form or nature of these observations is not reported by Tucker[2] and Palmer.[1] Ayman employed a questionnaire supplemented by a number of personal interviews.[3] Dunbar[5] relied mainly on case history material supplemented by interviews with some of her patients.

The number of subjects studied, however, was unusually large for psychiatric research. Ayman's[3] conclusions were based on observations of 95 subjects, Tucker's[2] on 100 cases, and both Palmer[1] and Gressel's group[6] on 50 cases. Dunbar[5] utilized information on 1,300 subjects without stating explicitly, however, how many of these cases formed the basis for her exposition of the "hypertensive personality."

One other methodologic problem inherent in much of this research is that control groups are not utilized in the sense in which they are most frequently employed in traditional psychologic and social research. The comparisons made are not between a study group and a control group. Rather, the comparisons are between various types of groups. For example, a group of hypertensive patients may be compared with a group of "coronary artery" patients. The discovery of certain psychologic characteristics among hypertensives which are not found among those suffering from coronary artery disease does not constitute adequate proof that these characteristics are unique to hypertension.

c. *The claim that the hypothesis is specific to the disorder of hypertension is not amply supported:* All of the investigators under discussion claim that their personality descriptions are specific to hypertension, i.e., they claim that these psychologic characteristics are unique to individuals who will be or are subject to hypertension. Other sets of psychologic factors have been described as specific to peptic ulcer, asthma, coronary artery disease, and other disease entities. However, no evidence is offered to support the implication that "healthy" individuals do not have these characteristics. A further point which is not clarified concerns just what it is that is claimed as specific. Logically, it cannot be the presence of some individual characteristic or action, because these appear in different combinations in the description of psychologic characteristics claimed

to be associated with other disorders. If it is the whole configuration which is claimed as specific, that is, the unique presence of a number of characteristics in their relation to each other, it becomes difficult to reconcile this with the already noted dissimilarities in the observations of different investigators.

d. *The psychologic components of the "hypertensive personality" are not described with sufficient precision to permit their objective measurement by independent investigators:* It is part of the everyday language to describe people as ambitious, conscientious, sensitive, serious, etc., and when these words are used, they undoubtedly communicate ideas which are commonly understood, at least in a general way. However, something more than common understanding of this indefinable sort is required in scientific communication. The identification of an individual as ambitious by one investigator cannot be confirmed by another unless he is aware of what the components of ambitiousness are conceived to be and how they are to be measured. For the most part, the investigators who have suggested the possibility of a "hypertensive personality" have not provided the kind of definition or explanation of the descriptive terms they use to permit verification by independent investigators.

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The exception is the work of Gressel and associates,[6] who do describe with some degree of explicitness what they mean by such behavior patterns as impulsiveness, subnormal assertiveness, or obsessive-compulsiveness. The four-point scales devised by them to measure the utilization of these patterns by the individual are capable of being administered independently. However, a difficulty arises here in the interpretation of the results obtained from administering these scales.

These difficulties make it impossible to incorporate the "hypertensive personality" hypothesis at its present stage of development in a long-term study of hypertension. More experimental work is obviously needed which would permit formulation of the hypothesis in such a way that it is capable of independent verification. A long-term field study of the kind contemplated is not the most suitable vehicle for accomplishing this objective.

2. *Psychologic Conflicts in Patients With Hypertension.*—In contrast to the preceding hypotheses on the "hypertensive personality," other investigators hold that hypertension is related to the inability of certain individuals effectively to resolve conflicting needs for dependency and for expressing aggressive feelings. Alexander[7] characterizes the conflict in the following manner: "This conflict consists [*sic*] between passive dependent, feminine receptive tendencies and over compensatory, aggressive, hostile impulses which lead to fear and increase a flight from competition towards the passive dependent attitude . . . characteristic for the hypertensive individual is his inability to relieve freely either one of the opposing tendencies. He can neither freely accept the passive dependent attitude or freely express his hostile impulses. A kind of emotional paralysis can be observed which results from the two opposing emotional attitudes blocking each other."

Robbins[8] writes about the typical conflict pattern in this way: "In order to relieve their anxiety and establish some feelings of security these patients would tend to suppress their hostile feeling resulting from their frustrations and

try to establish a passively dependent attachment to one or both of their parents. Fear of parental disapproval in retaliation for unacceptable behavior was quite marked, as was an inability to mobilize and express their aggressive impulses."

Hambling[9] states: "In using the word resentment for the psychological aspect of this hypertensive emotional state I have in mind the image of an aggressive anger welled in by constraint, a conflict part conscious, part unconscious . . . it seems to me that the multiple anxiety symptoms commonly encountered in hypertensives relate to the threatened outbreak of these aggressive impulses in subjects who cannot tolerate the loss of love that follows in the wake of verbal and muscular violence."

While postulating their hypotheses in different ways, there is a degree of consistency among these investigators which is not present among those of the "hypertensive personality" school. Furthermore, this view of psychologic conflict derives from, and is well grounded in, psychoanalytic theory. Unlike the "hypertensive personality" hypothesis, therefore, the "psychologic conflict" hypothesis is based on a relatively solid foundation of psychologic theory. However, for a number of reasons, the hypothesis cannot be accepted as verified to any extent.

a. *The evidence offered in support of the hypothesis is fragmentary:* The number of cases studied by exponents of this orientation are quite small and are drawn primarily from persons whose social backgrounds are middle class. Alexander's[7,10] formulation, for example, is based on the intensive study of two cases, Saul[11] studied seven individuals, and Hambling[9] based his conclusions on the study of four. The hypothesis regarding the nature of the specific conflict involved emerged primarily in the course of psychotherapy of individuals having hypertension. Methodologically, therefore, a question might be raised as to the justification for generalizing from these small samples. Furthermore, as in the case of the "hypertensive personality" approach, there is a notable failure to introduce control groups in tests of the hypothesis. Questions such as whether or not repressed hostility is a characteristic of individuals suffering from no serious physical or mental disorder, or the extent to which conflict between dependency and aggressive-competitive strivings do not also characterize individuals suffering from a host of other disorders, are not sufficiently explored. This problem, of course, is one which is fairly common to psychiatric methodology and does not arise especially from hypertension research.

b. *There is need for further definition of what form of psychologic conflict is claimed as specific to hypertension:* Conflict between dependent and assertive strivings is associated in psychoanalytic theory with many mental and physical disorders. It is suggested that where this conflict results in the complete inhibition of aggressive impulses, some form of hypertension will be latent or manifest in the individual. In other words, it is this particular manifestation of psychologic conflict that is considered specific to hypertension. However, our society defines as expected behavior for its members the responsible inhibition of aggressive propensities. It is difficult to know from these researches just what degree of inhibition is considered necessary to produce an associated physiologic disorder such as hypertension. The investigators under discussion do

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not define precisely the dimensions of behavior with which they deal. This leads to the final difficulty to be mentioned, namely:

c. *The hypothesis is not formulated in such a way as readily to permit its being tested objectively by independent investigators:* This criticism is similar to an earlier one leveled at the "hypertensive personality" hypothesis and is one which might be raised with respect to psychoanalytic theory generally. The difficulty is that these hypotheses are formulated in such a way that it becomes impossible to assess them in any more objective way than through the "trained intuition" of the psychotherapist. This is not intended to reflect on the creative contributions of the psychotherapist to our understanding of disease, but rather to suggest that the full implications of their work cannot be realized until some methodology is developed to permit common and objective examination of their concepts.

It is conceivable that a long-term epidemiologic study of hypertension might be a suitable vehicle for subjecting the "psychologic conflict" hypothesis to further examination. However, it is not feasible to do this through an extended and periodic psychiatric examination of many hundreds of subjects. The field study of psychologic conflicts would be facilitated by the development of objective tests and procedures which could be carried out under field conditions and the results of which would permit classification of each subject according to the kind and degree of psychologic conflict which he experiences. The first step in developing such an assessment procedure would involve obtaining a more adequate specification of what is meant by terms such as hostility, dependency, and receptive tendencies as they occur in hypotheses about hypertension. This means, in effect, getting the psychiatrist to identify precisely just what aspects of behavior he considers in classifying a subject as experiencing a conflict between his dependency needs and his aggressive propensities. Given such information, it should be possible to construct and standardize observational instruments which can be administered without difficulty by persons without the extensive knowledge of the psychiatrist.

3. Experiences of Stress.—The third set of psychologic factors thought to be related to hypertension have been variously described as stress, systematic stress, or emotional stress. The notion of stress, in the sense used here, refers to an event or experience in the life of an individual which has specific physiologic consequences. In general, these consequences are considered disturbances in the state of equilibrium of the organism such that, as Selye[14] puts it, "extensive regions of the body deviate from their normal resting state." A great variety of experiences or events have been identified as capable of engendering "stress"—illness or death in a family, for example, or surgery on oneself. Others include such experiences as a sudden separation from parents, loss of job, loss of savings, a setback in achieving one's ambition, or desertion by a supporting figure through infidelity, remarriage, suicide, or rejection in a will.

Altschule,[12] Reiser and others,[13] Selye,[14] Wolff,[15-17] and Harris and his group[18] have noted in the cases they have studied a frequent association between exposure to such stressful events and the onset of hypertension or temporary blood pressure rise. They have not, however, specified the conditions under which

such experiences produce a stressor response or indicated when hypertension will be the physiologic consequence of the experience. In other words, there is no claim that the experience of stress is specific to hypertension.

This hypothesis is obviously formulated in a less specific way than those previously discussed. It derives primarily from observations made by physicians on patients suffering from hypertension. Reiser and associates[13] base their formulation of the association on observations of 12 patients. Wolff[17] bases his conclusions on 89 cases. Other investigators do not report the number of cases studied. For the most part, investigators have based their conclusions on physiologic examinations combined with verbal reports from patients relating their pre-examination histories.

It is evident that in its present form the stress hypothesis does not contribute in any precise way to our understanding of the causes of hypertension. It does suggest, however, possibly fruitful lines for future research. What is needed, clearly, is further specification of the conditions under which a stressor response to events and experience in life occur and, more specifically, a definition of the way in which "stress" is associated with hypertension as compared with other disorders. A long-term study of hypertension seems a highly suitable way in which to accomplish these objectives. Since it envisions making observations on a population sample, a long-term study would permit a comparison of the way in which hypertensives and nonhypertensives respond to potentially stress-producing events in their lives. Furthermore, since the study would be conducted over a period of time, the temporal relationship of stress experiences to the development of hypertension could be carefully specified.

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THE MANNER OF ASSOCIATION OF PSYCHOLOGIC FACTORS WITH HYPERTENSION

Thus far, the discussion has centered on a simple description of the psychologic factors thought to be associated with hypertension. The emphasis has been placed on a specification of *what* is considered associated. In this section the discussion concerns the *manner* in which psychologic factors are conceived to be associated with hypertension. This includes assertions as to the direction of the association between one variable and another and the degree to which the two are causally related. It also includes in some instances the introduction of nonpsychologic variables as contributing and intervening factors.

Investigators vary in the degree to which they specify the manner of the association of the psychologic variable with hypertension. Some ignore the problem while others elaborate upon it in great detail. In the literature reviewed, it was possible to distinguish five different models of handling the matter.

1. The Sequences Involved Are Not Considered Explicitly in the Formulation of the Hypothesis.—With the notable exception of Dunbar,[5] the investigators advancing the idea of a "hypertensive personality" draw no explicit conclusions as to the way in which the chain of causation moves.* Implicitly, of course,

*Though Dunbar represents an example of the "Hypertensive Personality Profile" position, she has voiced definite views on the relationship of variables involved in the development of "psychosomatic disorders" generally. Thus, from her general position (referring not only to hypertension, but also to such other syndromes as peptic ulcer, coronary artery disease, etc.) one might deduce that her views would be adequately represented by Model No. 2, to be discussed presently.

there is an assumption that the personality configuration precedes and leads to the hypertensive disorder. At the same time, however, it is possible that the opposite may hold or, in fact, that both the psychologic characteristics and the hypertensive disorder are independently "initiated" by a third variable, for example, a set of physiologic factors such as the excess production of certain chemical substances in the organism.

The absence of an explicit assertion concerning the direction of the association undoubtedly derives from the methodology employed in this type of research. The subjects are ordinarily persons known to be hypertensive and, therefore, both the "personality configuration" and the disorder are recognized as "present" at the time of the observation. The establishment of the manner of the association clearly requires the extension of such research over a period of time among both hypertensives and nonhypertensives.

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2. The Psychologic Factors Precede and Are Responsible for the Physiologic Mechanisms Which Culminate in the Development of Hypertension.—Probably none of the investigators postulating an association between psychologic conflict and hypertension would consider himself an adherent of a strictly psychogenic view of the hypertensive disorder. However, some of them are not explicit about what other factors may be prerequisite; and their work consequently conveys the impression that psychologic conflict emerging from repressed aggression or the struggle between dependent and hostile tendencies is the only necessary precondition for the overstimulation of neuro-endocrine systems, resulting first in a temporary and then in a permanent elevation of blood pressure.

This inference concerning the direction of the association is supported by psychoanalytic and depth psychologic theory and by certain results of physiologic research, notably those obtained by Cannon and his students. Cannon's evidence that physiologic changes (adrenaline production, blood pressure rise, etc.) occur as a result of sustained states of anger and fear would seem to parallel the inference drawn here that hypertension results from sustained psychologic conflict. However, this claim of a direct causal link between psychologic conflict and hypertension cannot be accepted without further evidence based on studies done over a period of time that psychologic conflict alone can account for the onset of hypertension.

3. The Initial Conditions Are Provided by Genetic Factors With the Subsequent Introduction of Specified Psychologic Conditions Precipitating Physiologic Mechanisms Culminating in the Development of Hypertension.—This view is proposed by scientists oriented to viewing "psychologic conflict" or "stress" as associated with hypertension—men such as Binger,[19,20] Schur,[21] Wolff,[15-17] and Selye.[14] The genetic element enters into the sequence of causation at two points. It is present initially in the genetic disposition of the individual. The subsequent experience of psychologic conflict of a certain kind, or exposure to a stress-inducing situation, then leads to the release of physiologic mechanisms which by virtue of an inherent hereditary defect are unable to function "normally." Documentation for this position is seen, as provided by the evidence of a familial tendency to hypertension and by the propensity on the part of

offspring of one or two hypertensive parents to exhibit an exaggerated vasomotor response (as measured by the Hines cold pressor or Ayman-Goldshine breath-holding tests). However, it need be born in mind that familial occurrence—which affects a proportion of cases only—does not "prove" the primacy of genetic factors. For example, the occurrence of neurotic tendencies or that of fully developed neuroses is also familial in some instances. Unfortunately, no study has been undertaken to test directly the hypothesis that the experience of psychologic conflict or a stressor response on the part of individuals with hypertensive parents would indeed precipitate the onset of hypertension.

4. Particular Environmental Factors Are Prerequisite to the Experience of Psychologic Conditions Which in Turn Are Followed by Physiologic Mechanisms Culminating in Hypertension.—The fourth model encompasses the views of a number of physicians and psychiatrists who differ from each other in the substantive content of their work. Like the previous two models, it is also suggested by research dealing with the relationship between psychologic conflict or stress to hypertension. It is advanced in roughly similar ways by such men as Alexander,[7,10,22] Halliday,[23] Ruesch,[24,25] and Schulze and Schwab.[26]

The initial environmental factors are described with varying degrees of precision. On the one extreme are generalized statements, such as, for example, that the assumed low rate of hypertension among the Chinese is due to the absence of certain environmental conditions in Chinese culture which in other cultures serve as the first step in the progression to hypertension. In some cases, initial environmental conditions are specified somewhat further in relation to class, ethnic group, or occupation, or they may be more precisely characterized, as, for example, "social pressures of middle class life (which) require an unusual amount of self control while rewarding competitive and assertive behavior." In effect, what these descriptions signify is that particular forms of social environment establish the conditions for the development of psychologic disorders. In turn, these engender physiologic mechanisms which lead to the hypertensive state.

This view is supported primarily by evidence of the differential incidence of hypertension in various countries and for different racial, social, and occupational groups within countries. It is also based on the body of psychoanalytic theory suggesting that personality conflict and stressor experiences are the product of particular social or cultural conditions. Alexander's[7] work exemplifies this conception. He states, "[The individual is] confronted with the complex problem of maintaining his and his family's existence, his social position and prestige. In our present civilization all these tasks unavoidably involve hostile competitive feelings, create fears. . . ." Since not everyone living in the same environment or under equivalent social conditions develops psychologic disorders and, in turn, hypertension, it is evident that some additional variable must be introduced to account for these variations.

5. Physiologic Factors Are Primary. The Hypertensive Disorder as Well as Associated Psychologic Conditions Are Secondary Results of the Initial Presence of Specified Physiologic Factors.—The final model is perhaps the least clearly described in the literature. The investigators maintaining this position are

usually prone to ignore or overlook the possible psychologic component in hypertension. The physiologic variables mentioned are identified as metabolic disturbances or as a lesion in the central nervous system, tumors, etc. Factors of these kinds are claimed to set other physiologic mechanisms into motion leading to the development of hypertension and, at the same time, to lead to certain psychologic changes in the individual as well. However, the latter process is not clearly specified.

It would undoubtedly be unwise to discard this model from consideration as a possible explanation of the association of psychologic factors and hypertension. However, considerably more research directed specifically to evaluating it is required before any final judgment can be rendered.

SUMMARY AND CONCLUSIONS

This paper has dealt with the role of psychologic factors in hypertension. The discussion considers what associations between psychologic factors and hypertension have been postulated and then considers the manner of their association.

a. It is suggested that hypotheses as to the association between psychologic factors and hypertension can be placed into three classifications: those emphasizing the whole configuration of characteristics making up the so-called hypertensive personality; those considering specific psychologic conflicts as the unit of psychologic description; and those dealing with conditions of psychologic stress.

b. Research bearing on each of these general hypotheses has been described and evaluated from a methodologic standpoint.

c. Five different approaches to the manner in which psychologic factors are thought to be associated with hypertension have been discussed. These are:

1. The sequences involved are not considered explicitly in the formulation of the hypothesis.

2. The psychologic factors precede and are responsible for the physiologic mechanisms which culminate in the development of hypertension.

3. The initial conditions are provided by genetic factors with the subsequent introduction of specified psychologic conditions precipitating physiologic mechanisms culminating in the development of hypertension.

4. Particular environmental factors are prerequisite to the experience of psychologic conditions which in turn are followed by physiologic mechanisms culminating in hypertension.

5. Physiologic factors are primary. The hypertensive disorder as well as associated psychologic conditions are secondary results of the initial presence of specified physiologic factors.

From this appraisal of the literature, it seems plain that there is a sufficient basis for the proposition that psychologic factors play some role in the onset or development of hypertension to warrant its further exploration. The question is how this can be accomplished most effectively. Undoubtedly, a variety

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of approaches are feasible and worth trying. Among these it would appear that a long-term, epidemiologic study of hypertension could make a significant contribution in this regard. It seems clear that one of the primary weaknesses of current research in this area is that it fails to take the factor of time into account. A long-term study would seem to provide a means for coming to understand the temporal element in the various relationships of psychologic factors to hypertension which have been postulated. In addition, since such a study would involve observations of nonhypertensive as well as hypertensive individuals, the appropriate controls could be incorporated in its design.

It is evident, however, that formidable difficulties of definition and measurement remain to be solved before a study of psychologic factors can be fruitfully explored in a long-term study of hypertension. Research instruments applicable to field conditions which would allow the classification of subjects along a variety of psychologic dimensions are simply not available. Experimental studies of a complex kind, therefore, seem a prerequisite to the development of the kind of research instruments which would be required to make feasible the testing of the extant hypothesis on the psychologic component in hypertension in a long-term field study of the disorder.

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STUDIES IN HYPERTENSION

VI. Differences in the Distribution of Hypertension in Negroes and Whites: An Appraisal

Henry L. Lennard, Ph.D., and Charles Y. Glock, Ph.D.

New York, N. Y.

(Received for publication May 5, 1956.)

From the Division of Epidemiology, School of Public Health and Administrative Medicine of the Faculty of Medicine and the Bureau of Applied Social Research, Columbia University

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IT IS probable, as already indicated in the introductory paper of this series,[24] that social and demographic factors in hypertension can be examined more effectively by epidemiologic than by laboratory or clinical procedures. This, the sixth paper in the series, examines the evidence on differences in the racial distribution of hypertension and appraises the hypotheses offered to explain the differences found.

The principal purpose was to determine whether and in what way the factor of race should be taken into account in a long-term study of hypertension. The specific questions to which answers were sought are these: What is the evidence concerning the distribution of hypertension among Negroes and whites in the United States? What conclusions does this evidence permit concerning the relationship between race and the occurrence of hypertension? What hypotheses does past research offer to explain these relationships? What is the nature of the empirical evidence supporting these hypotheses? Which of them warrant further exploration? And, how can this further exploration be pursued most effectively, i.e., to what extent can it be incorporated into the design of a long-term study and where might it be pursued more effectively through alternative approaches?

THE SUBSTANCE OF THE EVIDENCE

The evidence to be examined on the distribution of hypertension among Negroes and whites in the United States is of two kinds. First, there are the many studies comparing the occurrence of hypertension among selected samples of Negroes and whites. Second, there is the information on causes of mortality derived from death certificates, which is published in statistical reports of the United States Government.

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The evidence of the first kind, taken at face value, would seem to support a definite conclusion that hypertension is considerably more prevalent among the samples of Negroes studied than among the samples of whites. This is true when the samples are compared as a whole and when the factors of age and sex are controlled. The extent of the differences found varies from study to study, as might be expected, since the samples are not uniform but the direction of the difference is consistent.

The volume of evidence of this kind is too great to present here. However, the following sample of quotations taken from a variety of studies of the problem help to document the general conclusion drawn.

"We found that hypertension occurred with much greater frequency in Negroes than among white men." (Kesilman.[1])

"Hypertensive heart disease, as seen in this dispensary is of two and a half times greater incidence in the Negro than in the white race. The incidence is 12.5 per cent for the Negro and 4.9 per cent for white patients." (Schwab and Schulze.[2])

"The incidence of hypertension was particularly high in the Negro race, and especially in the Negro male." (Langsam and Perry.[3])

"Among 1,000 Negro male factory workers in the Cincinnati area, 29.4 per cent had hypertension. Among 1,000 male white workers of the same age in the same community, 9.1 per cent had hypertension." (Cincinnati Heart Council Study.[4])

"In this study, Negroes constituted 8.7 per cent of the sample and 20.7 per cent of the hypertensives." (Reisinger.[5])

"In New York City I have observed that hypertension is more common in Negroes than in whites." (Fishberg.[6])

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It is to be noted that there is considerable variation among these investigators in definition, in procedure, and in sample selection. Some refer to "essential" hypertension, others to hypertensive heart disease, and still others to hypertensive cardiovascular disease. Furthermore, even among those who claim to be studying "essential" hypertension, there is disagreement over what constitutes hypertension. In some studies, a person whose systolic blood pressure is 160 mm. or over is considered hypertensive; others require evidence of cardiac enlargement as well as a blood pressure of at least this magnitude before diagnosing a person as hypertensive. Since there are no generally accepted criteria[24] as to what constitutes hypertension, it is not surprising that these variations in definition occur.

The studies also vary in the procedures used in taking blood pressure measurements and in making clinical diagnoses. Furthermore, it must be recognized that none of the studies comparing the occurrence of hypertension among Negroes and whites is based on samples representative of the population at large. Rather, they are studies of special population groups such as hospital patients, prisoners, industrial laborers, draftees, and so on.

Despite these variations in definition, in procedure, and in sample selection, and despite other inadequacies of somewhat less importance, it is nevertheless significant that these studies *all* support a similar conclusion; namely, that Negroes in the United States are more often found to suffer from essential hypertension, hypertensive heart disease, hypertensive cardiovascular disease, or

related disorders, than whites. In fact, in so far as is known, no study has been done on a group of subjects in the United States which would support an opposite conclusion.

Mortality statistics provide further support for this general conclusion. Although the data are open to some of the same criticisms mentioned for the morbidity studies, the consistency of the findings is impressive. The data, reported in Table I, show the death rate (per 100,000) from hypertension with and without mention of heart disease for the Negro and white inhabitants of the United States for 1950.* The table omits rates for Negro mortality in those states where the Negro population is less than 25,000.

Table I clearly shows that the Negro death rate from hypertension with and without mention of heart disease is higher than the white death rate for every state in which comparisons were made. In many states, the Negro death rate is from two to three times higher than the white death rate. This is true for both males and females.

The higher mortality from hypertension among the Negroes cannot be considered fully demonstrated, however, until the factor of age is taken into account. Table II presents the death rate from hypertension with and without mention of heart disease for the population of the United States by age, sex, and race.†

Table II strikingly demonstrates that the mortality of both Negro males and females is higher than that of white males and females for every age group between 20 and 84. Between the ages of 30 and 55, the Negro mortality is from five to nine times as high as the white mortality. This applies to hypertension with and without mention of heart disease. It should be noted that the magnitude of the differences between the Negroes and whites is similar for the two diagnostic groupings.

Like the data referred to earlier on the occurrence of hypertension among live subjects, the mortality data just presented cannot be accepted uncritically. The system of classification upon which present reporting is based went into effect only in 1948, and it is doubtful that it was being effectively and accurately followed by 1950. Furthermore, it must be recognized that death certificates are often filled out by persons who are not familiar with the medical history of the deceased individuals. Diagnosis of the cause of death, therefore, may be subject to a considerable error.

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*The category *hypertension without mention of heart disease* includes the following individual causes of death: (1) essential benign hypertension without mention of heart; (2) essential malignant hypertension without mention of heart; (3) hypertension with arteriolar nephrosclerosis without mention of heart; and (4) other hypertensive disease without mention of heart.

The category *hypertension with mention of heart disease* includes these causes of death: (1) essential benign hypertension with heart disease; (2) essential malignant hypertension with heart disease (3) hypertensive heart disease with arteriolar nephrosclerosis.

†The raw figures used for computation were taken from Vital Statistics of the United States, 1950, Vol. III, and the 1950 Population Census (PC 14, No. 13-19, Selected Summaries).

TABLE I. DEATH RATE FROM HYPERTENSION WITH AND WITHOUT MENTION OF HEART DISEASE BY RACE, SEX, AND STATE*

STATE (LISTED BY GEOGRAPHIC LOCATION)	HYPERTENSION WITH MENTION OF HEART DISEASE (DEATH RATE PER 100,000)				HYPERTENSION WITHOUT MENTION OF HEART DISEASE (DEATH RATE PER 100,000)			
	WHITE		NEGRO		WHITE		NEGRO	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Maine	44	66	—	—	9	12	—	—
New Hampshire	53	70	—	—	8	7	—	—
Vermont	43	47	—	—	14	10	—	—
Massachusetts	48	62	72	114	9	8	28	11
Rhode Island	58	74	—	—	11	10	—	—
Connecticut	49	64	59	115	7	7	8	15
New York	48	64	70	98	7	8	10	10
New Jersey	48	65	94	96	8	8	15	13
Pennsylvania	56	67	102	112	8	9	22	18
Ohio	51	58	87	109	9	8	15	20
Indiana	59	68	95	126	10	8	19	20
Illinois	54	63	99	127	9	8	17	16
Michigan	36	44	70	83	6	7	12	13
Wisconsin	39	49	—	—	7	8	—	—
Minnesota	41	48	—	—	10	11	—	—
Iowa	44	48	—	—	8	8	—	—
Missouri	56	58	178	165	11	8	30	29
North Dakota	36	49	—	—	12	10	—	—
South Dakota	36	37	—	—	7	7	—	—
Nebraska	47	49	—	—	6	6	—	—
Kansas	48	52	138	149	10	11	25	16
Delaware	87	107	—	—	8	5	—	—
Maryland	76	96	150	170	7	7	16	20
Dist. of Columbia	87	87	153	163	6	6	18	19
Virginia	46	52	102	110	7	5	17	20
West Virginia	43	43	118	96	9	7	14	11
North Carolina	49	46	105	112	7	5	16	11
South Carolina	57	50	133	108	9	5	17	8
Georgia	59	50	117	93	9	7	16	12
Florida	41	39	87	76	9	6	14	15
Kentucky	60	58	151	184	9	7	20	21
Tennessee	51	49	133	128	7	7	22	24
Alabama	55	54	119	98	8	5	15	19
Mississippi	53	51	92	92	10	6	11	9
Arkansas	49	42	79	67	9	7	14	14
Louisiana	41	47	105	120	7	5	17	18
Oklahoma	38	37	116	93	8	9	18	27
Texas	32	31	73	76	7	6	12	15
Montana	28	33	—	—	8	8	—	—
Idaho	27	34	—	—	5	7	—	—
Wyoming	25	29	—	—	4	7	—	—
Colorado	34	45	—	—	6	6	—	—
New Mexico	23	22	—	—	2	6	—	—
Arizona	35	23	—	—	7	5	—	—
Utah	36	40	—	—	4	5	—	—
Nevada	29	24	—	—	8	6	—	—
Washington	42	48	—	—	9	7	—	—
Oregon	57	66	—	—	5	5	—	—
California	46	50	85	83	7	6	9	10

*Source of data: Vital Statistics of the U. S., 1950, Vol. III. States where the total Negro male or female population does not exceed 25,000 are omitted from this table.

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TABLE II. DEATH RATE FROM HYPERTENSION WITH AND WITHOUT MENTION OF HEART DISEASE BY AGE, SEX, AND RACE FOR THE UNITED STATES (1950)*

RACE AND SEX	AGE (YEARS)											
	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–84
Hypertension With Mention of Heart Disease (Death Rate per 100,000)												
White												
Male	0.4	0.7	1.6	3.6	9.9	21.8	46.9	82.9	133.0	219.2	350.4	749.5
Female	0.3	0.7	1.6	3.8	10.5	21.6	42.4	69.0	124.9	207.5	371.8	748.9
Negro												
Male	2.3	5.0	15.3	35.5	74.5	125.5	252.9	366.2	491.4	545.9	778.4	1525.2
Female	2.4	5.9	23.5	48.7	98.1	164.2	274.8	398.0	540.3	498.1	789.2	949.5
Hypertension Without Mention of Heart Disease (Death Rate per 100,000)												
White												
Male	0.3	0.4	1.1	1.9	3.6	5.4	8.1	11.0	16.0	26.4	48.1	110.6
Female	0.2	0.5	1.0	1.4	2.9	3.3	5.4	6.7	12.3	21.1	40.5	106.0
Negro												
Male	1.2	3.5	9.2	15.0	20.9	24.7	34.1	32.2	55.7	62.5	84.0	141.7
Female	1.1	4.0	8.8	16.3	23.0	24.8	32.9	41.9	65.0	50.0	71.4	122.1

*Sources for the above data were (a) Vital Statistics of the United States, 1950, Vol. III, and (b) the 1950 Population Census (PC 14, No. 13-19, Selected Summaries).

Nevertheless, it would seem safe to say that the magnitude of the differences involved, their consistency for every age group, and their presence in every part of the country cannot be explained by reference to error and unreliability in recording the correct diagnosis.

INTERPRETATIONS OF THE OBSERVED DIFFERENCES

The existence of a greater propensity for the American Negro to be affected by and die from hypertension than the white would appear to be confirmed by the existing evidence. In any case, it is clear that a long-term epidemiologic study of hypertension could not overlook this evidence to the extent of omitting Negroes from the sample or of avoiding Negro-white comparisons in the analysis. However, it is obviously not enough to simply provide for Negro-white comparisons per se. In what ways are they to be compared? Or, put in another way, what additional information about Negroes and whites needs to be collected to come to an understanding through a long-term study or any other type of comparative study as to how these differences are to be explained?

The literature offers a wide variety of hypotheses and speculations to explain why Negroes in the United States are more likely than whites to be subject to hypertension. While much of what has been written or said is in a form which

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does not lend itself to systematic verification, there are a number of hypotheses warranting, in our opinion, further exploration. Some of these hypotheses are directed to a specific explanation of the Negro-white differences discussed above; others are of a more general nature but through extension include an attempt to explain the racial factor in hypertension. In the pages which follow, these hypotheses are described and the evidence offered in their support (or refutation) evaluated.* To simplify the discussion, the hypotheses to be reviewed have been labeled: the genetic hypothesis, the physical exertion hypothesis, the psychosomatic hypothesis, and the associated disorder hypothesis.

THE GENETIC HYPOTHESIS

Considerable research has been directed to determining whether there is an hereditary factor in hypertension. Researchers such as Søbye,[7] Schroeder,[8] and Ayman,[9,10] among others, claim that hypertension or a predisposition to hypertension is an inherited trait. Proceeding from this hypothesis, it is conceivable that the observed Negro-white differences in occurrence and mortality from hypertension may be explained by the different distribution of this trait in the Negro and white populations of the United States.

Whether this is, in fact, the case, however, is difficult to discover. Those who have had the most to do with exploring the possibility of an hereditary factor in hypertension cast no light on the matter since they have not considered race as a variable in their investigations. Comparable data on the Negro and white population of the United States over a number of generations is not available.

Another method of exploring this hypothesis lies in gathering data on the occurrence of hypertension among Negroes and whites living in other cultures and geographic areas. Presumably, a racial disposition to hypertension would be manifested in a higher occurrence of hypertension among Negroes than among whites wherever they may be located.

However, a review of the literature does not show this to be uniformly the case, though the evidence available is far from complete. Research on the African population is particularly contradictory in this regard. Some studies, those of Williams,[11] and Donnison,[12] for example, report lower rates of hypertension among particular African Negro tribes than among "comparable" white groups. Other studies, those undertaken by Becker,[13] for example, come to an opposite conclusion. Research on the occurrence of Negroes and whites residing in the West Indies[14] and Central America[15,16] present more consistent findings. The occurrence of hypertension among the Negroes living in these areas is reported as substantially higher than that of the native Indian populations and somewhat higher than that of the whites residing there.

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*These hypotheses are not taken directly from the literature but represent reformulations of existing hypotheses or extrapolations from them. It is not claimed that these are the only extant hypotheses on the racial factor in hypertension worthy of further investigation. They were selected for discussion in this paper since, as will be pointed out later, they can be most readily incorporated into a long-term study design.

This kind of evidence, however, even if it were wholly consistent with United States findings, does not eliminate the possibility that environmental rather than hereditary factors are responsible for the higher occurrence of hypertension among Negroes. In making cross-cultural comparisons of this kind, environmental influences are not automatically controlled. Negroes, particularly in the West Indies and Central America, are on the whole in a social position vis-à-vis the white population roughly comparable to that obtaining in the United States. It is quite possible that variables pertaining to the Negroes' social situation rather than their race per se is responsible for their greater apparent propensity to develop hypertension. Unfortunately, no comparisons holding social and economic status constant are available.

At the same time, however, the fact that there is a degree of consistency in these cross-cultural comparisons makes it difficult to reject the hereditary hypothesis altogether. Actually, more adequate grounds for doing so would exist if the results had proved to be highly inconsistent. Under such circumstances, the case for the role of environmental factors in hypertension would be immeasurably strengthened.

The dilemma, then, of determining whether or not an hereditary factor underlies differences in the occurrence of hypertension of Negroes and whites in the United States remains unresolved. What this implies for the direction of future research will be discussed in a later section. First, some alternative hypotheses offered as an explanation of these differences are considered.

THE PHYSICAL EXERTION HYPOTHESIS

A number of investigators[17,18] have pointed out that strenuous physical activity may result in temporary elevation of the blood pressure. Though there is apparently no research that demonstrates that excessive physical activity is capable of initiating the hypertensive disorder, the amount of physical exertion engaged in by hypertensive individuals is considered by some observers[6,18] to be an important factor in prognosis. The more physical work they do, the less favorable the prognosis. It is thus suggested that the Negro-white differences, especially with reference to mortality from hypertension, may be related to differences in the occupational distribution of Negroes and whites and, specifically, to the greater concentration of Negroes in occupations requiring physical exertion.

According to a recent study,[19] the Negro works in "the lowest paid and most menial occupations. He is concentrated in unskilled and semi-skilled work. These are the jobs that require long and strenuous muscular effort." These observations are supported by Labor Force Statistics, which show that in 1953, 26.2 per cent of Negro males in the labor force were employed as laborers while only 6.4 per cent of white males in the labor force were so employed. Among women, 41.4 per cent of the Negroes were employed as private household workers while only 5.1 per cent of the whites were employed in this capacity.[20] Further, with respect to the high Negro female mortality from hypertension, particularly hypertensive heart disease, it should be noted that the number of Negro females in the labor force increases up to the age of 44, while the number of white females in the labor force decreases after the age of 20.

The high Negro mortality from hypertension with and without mention of heart disease should also be considered in conjunction with the relatively low Negro mortality from coronary artery disease (less than 50 per cent of white mortality for the U. S. as a whole). Some recent English work on the low rate of coronary artery disease among physically active groups may be relevant here. The hypothesis advanced by Morris and his co-workers[21] is that "men in physically active jobs have a lower incidence of coronary heart disease in middle age than have men in physically inactive jobs. More important, the disease is not as severe in physically active workers tending . . . to have a smaller early fatality and lower early mortality rate."

Considering Morris' hypothesis together with the afore-mentioned physical exertion hypothesis, it is evident that the two reinforce each other. Thus, the greater Negro mortality from hypertension and his lesser mortality from coronary artery disease may both be explained as a function of his greater participation in physically demanding employment.

This kind of inferential evidence cannot, of course, be accepted as confirming the physical exertion hypothesis. However, it does suggest that the hypothesis deserves further exploration.

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THE PSYCHOSOMATIC HYPOTHESIS

An increasing number of researchers have classified hypertension among the psychosomatic disorders. Such classification implies that social and psychologic variables play a significant role in the etiology, development, and course of the disorder. Two types of variables are usually emphasized: (a) psychologic conflicts which the individual experiences and which grow out of his handling of aggressive feelings and (b) severe emotional stress conditioned by one or more of the variety of social contexts in which the individual lives: his family life, his work, or his leisure-time pursuits.

The observation that the Negro in America is subject to different kinds of social and psychologic pressures from the white would scarcely seem to need documentation. Surprisingly, however, little attention has been given to systematic investigation of what these differences are and how they are manifested in the personality configurations of the two groups. It would seem obvious, for example, that as a result of his social position vis-à-vis the white, the Negro would be more likely on the average to experience feelings of aggression and at the same time to feel constrained to repress them. However, it is difficult to locate any research on this subject in the literature. Kardiner, in a psychoanalytic study of Negro personality,[22] writes, "The Negro is trained by experience from earliest childhood in the suppression of aggression . . . watchfulness over this aggression is a constant preoccupation with every Negro." Kardiner's study, however, is based on intensive interviews with but 24 subjects.

Still less is known on what influence the peculiar social and psychologic situation of the Negro in the United States may have on his physiologic health. The possibility that the Negro's greater propensity to hypertension may be related to social and psychologic factors growing out of his environment would, nevertheless, appear to be a hypothesis justifying continued study.

THE ASSOCIATED DISORDER HYPOTHESIS

One final hypothesis might be added to this list, though it is perhaps the least well-documented of those that have been discussed. This is the possibility that the Negro-white differences under discussion may be explained by the greater occurrence of other disorders among the Negro: disorders which are associated with or lead to hypertension.

From time to time, it has been proposed that there is a direct relationship between the development of hypertension and the presence of other disorders, e.g., syphilis or pyelonephritis in the individual. Unfortunately, the several studies which have been undertaken to explore this hypothesis offer contradictory results.[6] It is useful, nevertheless, to consider the matter as still open since whatever future research is done on the racial factor in hypertension might readily incorporate the further examination of this hypothesis in its design.

SUMMARY AND CONCLUSIONS

This paper has examined the evidence on differences in the racial distribution of hypertension in Negroes and whites and appraises the hypotheses offered to explain the differences found.

a. Despite variations in definition, in procedure, and in sample selection, all studies examined support the conclusion that Negroes in the United States more often have essential hypertension, hypertensive heart disease, hypertensive cardiovascular disease, or related disorders, than whites.

b. The mortality of Negro males and females from hypertension, with or without mention of heart disease, is higher than that of white males and females for every age group between 20 and 84. Between the ages of 30 and 55, the Negro mortality is from five to nine times as high as the white mortality.

c. Four hypotheses offered to explain the racial differences are described and evaluated. These hypotheses were labeled: the genetic hypothesis, the physical exertion hypothesis, the psychosomatic hypothesis, and the associated disorder hypothesis.

It can be said that the evidence presented on the occurrence and mortality from hypertension among Negroes and whites is generally consistent with all of the major hypotheses which have been advanced. While relating the evidence to the hypotheses does not confirm them, neither does it refute them. Rather, it encourages further study utilizing the observed Negro-white differences as a point of departure.

It is clear, first of all, that field research is needed to complement laboratory and clinical studies. There is a need for research on representative samples of the population and for research which collects data on nonhypertensives as well as well as on hypertensive subjects. The former is necessary to permit generalizing the findings of research; the latter to make it possible to isolate those characteristics which are unique to the hypertensive.

Second, it would seem desirable in formulating research designs to consider ways of testing the interrelationship between sets of hypotheses rather than to focus research on the testing of a single hypothesis. In the present case, for

example, any study of the hereditary factor in hypertension should consider at the same time the contribution of social and psychologic factors to the disorder. It is unlikely that either hypothesis can be confirmed or refuted if studied in isolation.

Third, investigators should take into account the slow development and chronic character of hypertension and consider the need to establish the temporal factor in any relationships that are discovered. Knowledge, for example, that hypertensive individuals are likely to experience unique psychologic difficulties and, in turn, that Negroes are more likely to have these difficulties than whites is incomplete knowledge. The temporal sequence between the two must also be ascertained.

The hypotheses presented in this review are among those to be tested in a long-term study of hypertension, which is outlined in the first of this series of papers.[24] Research of this kind which envisions observing a large representative sample of individuals over a period of time would provide, it is believed, a suitable frame for further study of the Negro-white differences discussed above. It would require, to be sure, an oversampling of Negroes to make for valid Negro-white comparisons. However, it would provide for the simultaneous testing of the hypotheses offered to explain these differences. Thus, to test the genetic hypothesis, arrangements could be made to include several generations of the same family in the sample. Regular and systematic observations could be made to measure the amount of physical exertion expended by each subject. Batteries of psychologic tests could be administered to the subjects, and indices of the social conditions under which they live could be readily obtained. Periodic medical examinations of the sample would provide the kind of data necessary to test the associated disorder hypothesis. Finally, a long-term study could make a significant contribution to the further specification and definition of what hypertension is and what it involves.*

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*Other hypotheses on racial and demographic variables in hypertension would be examined also in the same manner as those included in this paper. These are specified in the first paper of this series.

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THE RELATION OF SYMPTOMS TO OSTEOARTHRITIS*

SIDNEY COBB, M.D., M.P.H., W. R. MERCHANT, M.D., AND
THEODORE RUBIN, PH.D.

PITTSBURGH, PA.

From the Graduate School of Public Health, University of Pittsburgh

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IT HAS long been recognized that many persons have x-ray evidence of osteoarthritis without symptoms. Recently this problem has received increasing attention,[1-5] even to the point where one author asks the question, "Do bony spurs cause pain?"[6] In the course of the population studies in Pittsburgh, this problem has forced itself on our attention because it appears that only 30 per cent of those with marked osteoarthritic changes on x-ray have had pain at the relevant sites in the past five years. We have sought an explanation for this phenomenon.

METHODS

In our population studies, the structure of which is adequately outlined in earlier papers in this series,[7,8] we recorded among other things the following observations which are pertinent to this subject:

1. History of nontraumatic joint pain in past five years.
2. Observed pain on motion of joints.
3. Observed joint tenderness.

These three items were summed to give a pain score which could reach a maximum of three if all were present. In addition, we recorded:

4. History of joint swelling.
5. Observed joint swelling.
6. Osteoarthritic changes by x-ray.
7. Morning stiffness.

Of these, the last requires specific comment for it is important that there be no semantic difficulties in this discussion. When we refer to morning stiffness,[9] we mean stiffness, numbness, or weakness in any group of joints or muscles that is noted on awakening and tends to pass off as the individual becomes active. We had two opportunities to inquire about the phenomenon for each of the individuals with whom we are here concerned.

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The group of persons studied comprises a stratified random sample of persons from the Arsenal Health District of Pittsburgh. Of the 478 persons examined, 115 were found, by x-ray, to have marked osteoarthritis in their hands or wrists and 65 were found to have marked changes in their knees. All the figures presented here are population estimates based on appropriate weighting of persons in the several strata.

RESULTS

The first approach to this problem has been to test the hypothesis[10] that the symptom of morning stiffness and degenerative changes by x-ray are quite independent. This has been examined from several points of view and the results are consistent with the hypothesis of independence. With this in mind, we can proceed to examine the relationships that are exhibited between these two independent variables and joint pain. The question is too diffuse unless examined on a site-specific basis for pain and degenerative changes. Since morning stiffness is considered to be a generalized phenomenon even though the patient may point out an area where it is worst, this is not considered on a site- or joint-specific basis.

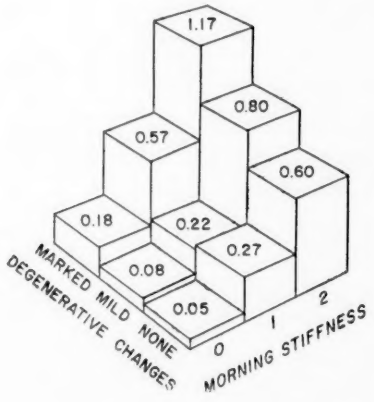

Fig. 1.—Average pain score for the hands and wrists as a function of degenerative changes by x-ray and morning stiffness.

The first site to be considered includes the hands and wrists. In Fig. 1 are shown the relationships between degenerative changes visible on x-ray, morning stiffness, and pain score for this site. The average pain score of each of the nine groups, into which the population is divided, is indicated by the height of the column and the number inscribed on the top thereof. Inspection of this figure reveals that morning stiffness has a greater association with pain score than do degenerative changes detectable by x-ray. To be more specific, an increase from no degenerative changes to marked degenerative changes produces a two- to threefold increase in pain score whereas progression from no report of morning stiffness to report of morning stiffness on both of the possible occasions produces

an increase in pain score ranging from six- to twelvefold. Fig. 2 shows a similar diagram for the knees. Here again the relationship between morning stiffness and pain score is clear though it should be noted that morning stiffness is not so dominant over degenerative changes at this site.

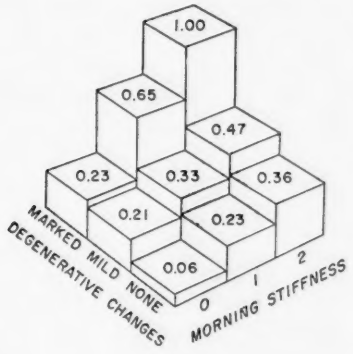

Fig. 2.—Average pain score for the knees as a function of degenerative changes by x-ray and morning stiffness.

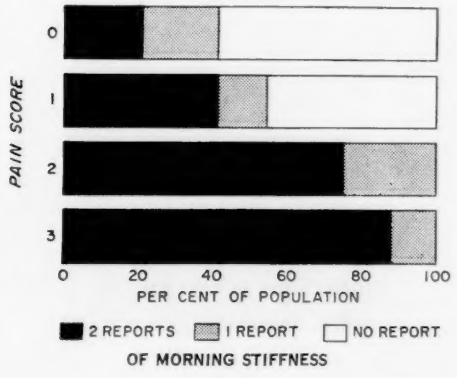

Fig. 3.—The relationship between pain in hands and wrists and morning stiffness among those with marked degenerative changes by x-ray.

In Fig. 3, attention is focused on those with marked degenerative changes by x-ray in their hands or wrists. Here the individuals are separated according to pain score, and the proportion of morning stiffness in each group is indicated by the amount of shading. It is clear that as pain increases morning stiffness also increases. In fact, there appear to be no persons with a pain score of two or more who do not have at least one report of morning stiffness. In Fig. 4, the same general relationship is illustrated for the knees. It should be noted that here pain scores of two and three have been combined in one group because the numbers are small.

With respect to swelling, Fig. 5 shows the relationship between swelling in the hands or wrists and morning stiffness among those persons who have x-ray evidence of marked degenerative changes at these sites. Apparently swelling does not occur in the hands or wrists without at least one report of morning stiffness. In Fig. 6, it can be seen that this is not true for the knees where we get a history of swelling in a few people who do not give a history of morning stiffness. Again it is important to remind the reader that the number of persons with swelling in the knees is fairly small (eight with history only and nine with observed swelling) and the estimates of the proportions with morning stiffness are not very reliable.

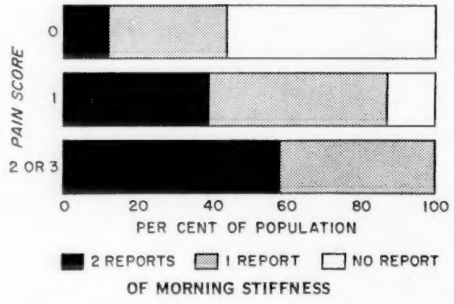

Fig. 4.—The relationship between pain in knees and morning stiffness among those with marked degenerative changes by x-ray.

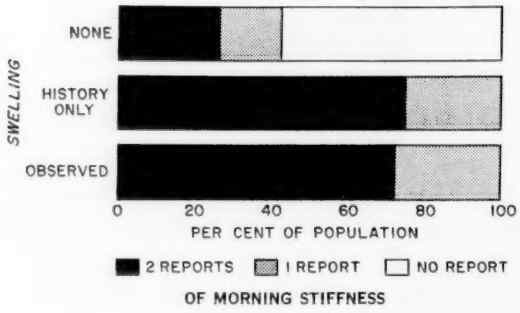

Fig. 5.—The relationship between swelling in hands or wrists and morning stiffness among those with marked degenerative changes by x-ray.

The emphasis so far has been on proportional relationships; it is therefore appropriate to turn our attention to estimates of the frequency of these various manifestations in the population of persons with osteoarthritic changes by x-ray. These are graphically displayed in Fig. 7. The previous point that morning stiffness is more common among those with local symptoms is seen again. But, in addition, it is now seen that persons without any morning stiffness have a

rather small chance of having local symptoms with their degenerative changes. One might ask why this expectation is larger for the hands than for the knees. The answer seems to be that the bulk of the symptoms in the hands among those with no morning stiffness are attributable to acute Heberden's nodes which as far as we can determine are unrelated to morning stiffness.

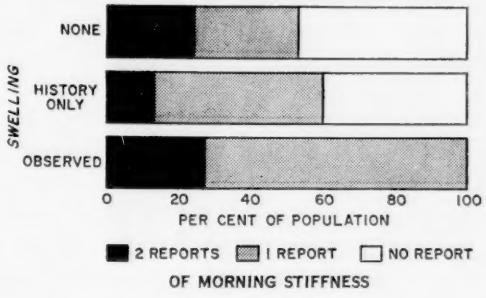

Fig. 6.—The relationship between swelling in knees and morning stiffness among those with marked degenerative changes by x-ray.

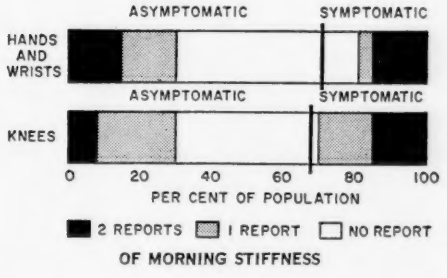

Fig. 7.—The distribution of persons with x-ray evidence of osteoarthritis in hand and wrists or knees according to the presence or absence of local symptoms and morning stiffness.

At this point it is useful to examine in more detail the symptom patterns of those without morning stiffness as compared to those with morning stiffness. First, among those with no morning stiffness, the average age at which the first joint pain occurred is 53 which is seven years later than for those with morning stiffness. In addition, those with no morning stiffness give an average lifetime history of only 3.7 painful joints as opposed to 4.6 painful joints for those with morning stiffness. When it comes to swelling, those with no morning stiffness average only 0.5 swollen joints per person compared to 1.4 joints swollen per person with morning stiffness. When we realize that the number of swollen joints per person with no morning stiffness would drop to 0.1 if we should exclude an attack of acute rheumatic fever in childhood and a single attack of "trench rheumatism" during World War I, it is apparent that recent joint swelling is infrequent among those free of morning stiffness. Having already seen in Figs.

5 and 6 that all the persons with observed swelling had at least one report of morning stiffness, we know that in this experience, at least, joint swelling at these sites was not observed in the absence of morning stiffness. While duration of attacks was not measured quantitatively, it is our impression that the group with x-ray changes and pain alone had rather short attacks, frequently precipitated by weather or excess exertion. On the other hand, in the group with morning stiffness, attacks usually lasted for several weeks and many patients were only rarely free of at least minimal joint discomfort.

Taking the opposite approach to this problem, we might say that, when compared with those free of morning stiffness, those with morning stiffness have their onsets of arthritis earlier in life, have a greater number of miscellaneous peripheral joints involved, are far more likely to have joint swelling, and describe the duration of their attacks of pain in terms of weeks rather than days or hours.

In a younger age group, this symptom pattern might be ascribed to mild rheumatoid arthritis. With that thought in mind, we have classified the group with symptomatic osteoarthritis and morning stiffness on the American Rheumatism Association criteria for the diagnosis of rheumatoid arthritis. This reveals, as one might expect, that there are in this group a few cases of definite rheumatoid arthritis which obviously are diagnosed as mixed rheumatoid and osteoarthritis, but the surprising thing is that 26 per cent meet the criteria for probable rheumatoid arthritis and 41 per cent meet the criteria for possible rheumatoid arthritis, leaving only 24 per cent who have morning stiffness but no other evidence of rheumatoid arthritis. Yet, these are all cases that would in ordinary practice be mostly diagnosed as osteoarthritis. On initial examination, we so diagnosed most of them; a few were left as unclassified and a fair number were given mixed diagnoses, but our basic impression of the group was one of osteoarthritis. Having completed this analysis, we are inclined to believe that the basic problem for most of this group is really rheumatoid arthritis and the osteoarthritic changes seen by x-ray are in many instances just incidental. In view of the fact that there is no specific test for mild or early rheumatoid arthritis, some observers might prefer less definitive terminology, such as fibrositis. However, our use of the specific term, rheumatoid arthritis, clearly expresses our current attitude on this subject.

Looking back to Fig. 7, it is seen that persons with x-ray evidence of osteoarthritis must be divided into two groups, the asymptomatic and the symptomatic. Those with symptoms as we have just seen may be further roughly subdivided into three groups. The first group is composed of those with no morning stiffness whose symptoms come late in life, are mild, transient, and usually without swelling, and are frequently associated with painful Heberden's nodes. The second group comprises those patients with morning stiffness whose symptom pattern is more that of fibrositis, myositis, or bursitis and who, when detailed histories and physical examinations are completed, actually meet the accepted criteria for possible or probable rheumatoid arthritis three quarters of the time. The third group is composed of those who have obvious rheumatoid or other arthritis and who incidentally have x-ray evidence of degenerative changes in their joints.

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DISCUSSION

As reported earlier,[11] only 60 per cent of the named sample was actually examined. The remainder either refused or had died or moved out of the county. It would seem possible, therefore, that the fallacy described by Berkson[12] might account for the conclusions reached. Fortunately, the interview which was conducted by nonmedical interviewers on a standard form, with instructions that each question was to be asked as printed, had a much higher completion rate (89 per cent). It covered the same individuals to whom examinations were made available so that some detailed information with regard to certain manifestations of arthritis is available for those who did not participate. A study of this material reveals that the bias that exists tends to have produced an underestimate of the association between morning stiffness and pain and an underestimate of the proportion of persons who are symptom free. Therefore, appropriate allowance for the known bias would strengthen the conclusions drawn.

Much emphasis has been laid on the symptom of morning stiffness in this discussion, for we feel that it is an important manifestation of rheumatoid arthritis,[9] and as previously postulated,[10] it has been demonstrated to be independent of x-ray demonstrable osteoarthritic changes. This symptom is sometimes difficult to elicit for it is variously described as stiffness, numbness, weakness, aching, or other discomfort. In addition, it is difficult to evaluate for, like the disease with which it is associated, it has exacerbations and remissions. On the one hand, one practically never obtains a history of morning stiffness in the past unless the person is currently afflicted; and on the other hand, we well remember the patient who reported morning stiffness on two occasions and a year later denied that he had ever been so afflicted. These three factors combine to make it imperative that repeated questioning be used to evaluate whether a given individual has this symptom continuously, intermittently, or never.

The findings of this study should, of course, be verified by others. It is important that full cognizance be taken of the dangers of Berkson's[12] fallacy in planning further studies, for the bias of this sort that is present in ordinary clinic material is so great as to preclude any well-rounded conclusions. Of course, the observation that joint inflammation in osteoarthritis is rare without morning stiffness can be examined in populations drawn from arthritis clinics or from private practice, although the conclusions drawn will not necessarily be valid outside the group under study. Our converse conclusion, which is equally important, that osteoarthritic joints are rarely inflamed in the absence of morning stiffness can only be re-examined in population studies. It is, therefore, important that further epidemiologic work be undertaken by other groups in order to check these findings.

SUMMARY AND CONCLUSIONS

1. Morning stiffness and x-ray evidence of osteoarthritis do not show evidence of association in this population study.

2. Only about 30 per cent of persons with radiologic evidence of degenerative changes in their joints complained of pain at the relevant sites.

3. Pain and swelling in osteoarthritic joints are seldom found without morning stiffness. The exception to this of course is found in the acute Heberden's node. It should be remembered in this connection that one inquiry about morning stiffness is often insufficient to pick up this manifestation.

4. Persons with x-ray evidence of osteoarthritis but no morning stiffness have only a small chance of having pain at the relevant sites.

5. The importance of distinguishing symptomatic and asymptomatic osteoarthritis has been emphasized and the difference in symptom pattern between those with morning stiffness and the relatively few without it has been presented.

6. The possibility that most of the symptoms of "osteoarthritis" are at least in part due to a rheumatoid component has been discussed.

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PRIMARY CARCINOMA OF THE LIVER

Review of the Literature and an Analysis of Twelve Additional Cases

Daniel J. Thompson, M.D., Donna J. Hackley, M.D., and
Charles M. McGinnis, M.D.

Tuskegee, Ala.

From the Department of Internal Medicine, Veterans Administration Hospital, Tuskegee, Ala.

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INTRODUCTION

PRIMARY carcinoma of the liver is rare in America and Western Europe. It is much more prevalent in Africa and in certain oriental countries such as China, Japan, Formosa, and Java. An extensive review of the literature by Charache[10] in 1939 revealed that 808 cases of primary carcinoma of the liver had been recorded in 159,762 autopsies from hospitals throughout the world. Five years later Warvi[17] collected 1,200 cases of this disease after eliminating 16 of Charache's as reduplications. In 1950, Carnahan[27] reviewed the literature and found 1,391 cases of primary liver carcinoma. In our recent review of the literature a total of 2,205 cases were found (see Table I).

The purpose of this paper is: (1) to review briefly the subject of primary carcinoma of the liver, with special reference to racial susceptibility, and to recent documented cases in the literature which tend to suggest a higher rate of occurrence of this disease in the United States than is indicated by less recent reports; (2) to report 12 additional cases of this disease which were discovered in the course of 715 consecutive autopsies and by the performance of 4 liver biopsies on Negro male veterans at the Veterans Administration Hospital, Tuskegee, Alabama; (3) to call attention to the prevalence of hepatoma and the relative paucity of cirrhosis in these cases; and (4) to call attention further to a possible significant relationship between mode of living and the development of primary hepatic carcinoma.

ETIOLOGY AND RELATIVE FREQUENCY OF THE DISEASE

Although the etiology of primary carcinoma of the liver is not known, various theories have been advanced by investigators as a result of accumulated experimental data and clinical experience. Strong, Pitts, and McPhee[25] have observed that the disease is often found in Chinese who have been infested previously with the intestinal parasite, *Clonorchis sinensis*. They believe that this parasite produces irritation of the liver, resulting in hepatitis and cirrhosis and the eventual evolution of primary hepatic carcinoma. In the cases reported

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE I. TABULATED DATA OF A GENERAL NATURE RELATIVE TO THE 12 CASES OF PRIMARY LIVER CARCINOMA REPORTED AT THIS TIME

CASE	AGE (YR.)	OCCUPATION	NUTRITION HISTORY	ALCOHOLISM	ONSET OF SYMPTOMS TO DEATH (MONTHS)	CLINICAL DIAGNOSIS	PATH. DIAGNOSIS	LIVER WEIGHT (GRAMS)
W. J.	56	Sawmill worker	Adequate	Admitted excess use	4	Diverticulitis of colon with peritonitis	Hepatoma	3,900
G.M.L.	57	Carpenter's helper	Adequate	Denied	10	CA of cecum, cirrhosis R.O. amebic hepatitis	Hepatoma	
S.D.	32	Chauffeur	Adequate	Denied	11	Chronic gastritis	Hepatoma	
C.P.	58	None given	Adequate	Occasional moderate	8	Primary hepatoma, cirrhosis	Hepatoma	
W.O.	60	Former miner	Adequate	Moderate	4	HCVD* with congestive failure	Cholangioma, biliary cirrhosis	2,750
J.U.	30	Grocery clerk	Inadequate	Excess admitted	4–5	Cirrhosis of liver	Hepatoma	4,700
H.R.	32	Sawmill worker	Adequate	Excess admitted	2	Cirrhosis of liver with subacute hepatitis	Hepatoma	5,250
J.R.	55	Former laborer	Adequate	No data	5	CA of pancreas with metastasis to liver	Hepatoma	2,625
V.B.	55	Common laborer	Adequate	Denied	12	CA of stomach with metastasis to liver	Hepatoma	
E.H.	63	Const. worker	Adequate	Infrequent small amount	1–5	CA of stomach with metastasis to liver	Hepatoma, cirrhosis	3,250
S.B.	54	Former farmer	Adequate	No data	2	Metastatic CA of liver probably from stomach	Hepatoma	3,600
B.B.	60	Former farmer	Inadequate	Excess admitted	3	Primary CA of liver, Laennec's cirrhosis	Cholangioma, cirrhosis	3,250

*Hypertensive cardiovascular disease.

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by Tull,[5] infestation with liver flukes and dietary deficiencies were prominent. A recent report by Berman[42] emphasizes the prevalence of malnutrition in the Bantu natives of South Africa, who seem to be peculiarly susceptible to primary liver carcinoma. It is of interest that protein intake has been noted to be inadequate in these, as well as in other reported instances of patients with histologic evidence of primary hepatic carcinoma. This strongly suggests a possible causal relationship between nutritional status and the development of this disease in certain patients. Even greater impetus is given to the theory by the fact that cirrhosis has been demonstrated in a majority of patients with primary liver carcinoma,[14,20,32] since the former is thought to be brought about by nutritional deficiency.

Exposure to certain toxic substances may result in the development of cirrhosis of the liver, and a few investigators[20,26] are of the opinion that if exposure is continued long enough, neoplastic changes may occur in the hepatic cell. The azo dyes, ortho-azo-toluene, "butter yellow," and acetyl-aminofluorene have been employed to produce hepatomas in certain rodents. Trauma, alcoholism, cirrhosis, malaria, syphilis, and parasitic infestations are listed by Greene[11] as possible factors contributing to the development of primary carcinoma of the liver. Boyce and McFetridge[6] found some evidence of preceding syphilitic infection in 19 of the 28 cases they reported.

Lemmer[28] states that primary carcinoma of the liver is a disease of older people. Although he reported only 19 cases, the bulk of the evidence in the literature tends to support the impression that the disease generally is much more prevalent in older individuals. The majority of reported cases are in the sixth decade. Berman,[42] however, reports that the disease among Africans and Indonesians occurs pre-eminently in the young, chiefly below the age of 40 years. There are other documented case reports of the disease in individuals between the ages of 4 months and 83 years.[15,39] Steiner[9] collected 77 cases of the disease in children under 16 years of age; and of this number, 53.2 per cent were less than 2 years of age. Since the disease has been found in infants, it has been suggested that embryonic cell rests in some way may lead to the development of primary liver carcinoma.

The autopsy rate for primary carcinoma of the liver in the United States has been said to be less than 0.5 per cent of all hospital autopsies, and the average rate is said to be about 0.25 per cent.[8,20,35,37] In certain sections of the Orient and in Africa, this figure exceeds 1 per cent. Recent reports[19,23,38,40] in the United States seem to indicate that primary hepatic carcinoma may be much more prevalent here than previously accepted figures seem to indicate. Schupbach and Chappell[38] reported 14 cases found in 797 consecutive autopsies in male veterans at Kennedy Veterans Administration Hospital in Memphis, Tennessee. Primary liver carcinoma, therefore, occurred in 1.76 per cent of their adult autopsies. An autopsy rate of 1.06 per cent was reported by Galluzzi and others[40] in their review of 19 cases of this disease at the United States Public Health Service Hospital at Staten Island, New York. Holley and Pierson[23] reported 5 cases of primary carcinoma of the liver in 500 consecutive autopsies, a rate of 1 per cent.

PATHOLOGY

Primary hepatic carcinomas consist of the hepatoma or liver-cell type, the cholangioma or bile-cell type, and a mixed type with pathologic features of both.[14] The hepatoma is about five times more prevalent than the cholangioma and may occur as a single large tumor or as a few to many small tumors scattered throughout the liver. The cholangioma usually forms multiple adenomatous nodules throughout the liver. Necrosis and hemorrhage in the carcinomatous nodules frequently occur. The liver is usually stained with bile due to the obstruction of the normal biliary passages.

The co-existence of cirrhosis and primary carcinoma of the liver in the same patient has long been recognized as a likely occurrence. Numerous reports indicate that the relative frequency with which these two diseases occur together in a given patient is significantly high. Jaffe[3] stated 90 per cent of all primary carcinomas of the liver are associated with cirrhosis. Strong, Pitts, and McPhee[25] reported the presence of cirrhosis in 87.2 per cent of the 55 cases they studied. Webb[19] recorded the presence of cirrhosis in all of the 12 cases he reported. Schupbach and Chappell[38] reported 57 per cent of their 14 patients had cirrhosis. True atrophic cirrhosis was reported by Blatchford[35] in 3 of 14 patients, representing 21.4 per cent of the group. Four additional cases of biliary cirrhosis were noted also. This author states that the percentage of cases of true Laennec's cirrhosis in some of the reports of primary liver carcinoma in the literature may be considerably less than recorded figures indicate; and he attributes the possible discrepancy to the probability that cases of biliary cirrhosis are included in some instances. In general, the cholangioma is said to be less often associated with cirrhosis.

It has been stated that primary hepatic carcinoma has less tendency to metastasize to distant organs, especially bone, than other types of primary carcinoma.[4,14,16] However, hepatoma seems to have a greater tendency to metastasize distantly than does cholangioma. The most frequent site of metastatic involvement is the lungs. The second most frequent site is the mediastinal lymph nodes. Other reported metastatic sites include periportal lymph nodes, diaphragm, peritoneum, omentum, adrenals, pancreas, spleen, stomach, vertebrae, skull, ribs, brain, heart, kidney, pericardium, pleura, long bones, epidural space, spinal cord, and prostate. Charache[10] found metastasis to bone in only 1.6 per cent of the 1,125 cases he reviewed. Greene[11] reported bone metastasis in 8 per cent of the 386 cases he studied; and Carnahan[27] reported bone metastasis in 45 of the 1,391 cases he collected from the literature.

SYMPTOMS, SIGNS, AND PROGNOSIS

Symptoms of primary carcinoma of the liver are vague, and may be similar to those caused by metastatic lesions from primary carcinoma of other organs or by other nonmalignant disease processes. The majority of patients with primary liver carcinoma live only about 3 to 8 months after the onset of symptoms; although a few have been followed for a year or more before death. Sanford[37] reported that duration of the disease from onset of symptoms to death ranged from 5 days to 6 years in the 38 patients he studied.

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The patient usually complains of vague abdominal pain, weakness, weight loss, anorexia, nausea, and vomiting. Abdominal pain may not be complained of until it is severe or until a palpable mass in the upper abdomen is detected by the patient. Cirrhosis of the liver alone also may give rise to such symptoms; but increasing cachexia, and progressive liver enlargement[26] are usually more prominent in primary carcinoma of the liver. It has also been stated that weight loss, though usually present, frequently may not be as striking as in other malignancies.

Strong, Pitts, and McPhee[25] found ascites and hepatomegaly to be the most common signs in their patients. In Greene's 386 patients, 66 per cent had ascites, 48 per cent hepatomegaly, and 52 per cent were jaundiced.[11] Tull[5] found ascites in 48 per cent, hepatomegaly in 15 per cent, and jaundice in 34 per cent of his 134 patients. Warvi's analysis of 400 cases in the literature revealed ascites in 46 per cent, jaundice in 38 per cent, and hepatomegaly in 12 per cent.[17] Although liver enlargement was recorded in only 15 per cent of Tull's patients and 12 per cent of those in Warvi's review, in both groups palpable tumors were recorded in 68 per cent of the patients.

Most authors agree that there is little fever in patients with primary hepatic carcinoma until the terminal phase, when a rise to about 101° F. may be noted. This temperature rise has been thought to be caused by hepatic necrosis, although bronchopneumonia and other conditions may be contributory in some instances.

Splenomegaly and vascular spiders (angiomata) are seen in some cases in which there is considerable portal obstruction as a result of atrophic cirrhosis. Greene[11] noted splenomegaly in 34 per cent of the 386 cases he reviewed.

Elevation of the right hemidiaphragm occurs in some cases of primary carcinoma of the liver; but, obviously, this finding cannot be considered as pathognomonic, since it may be seen in numerous other conditions affecting the liver or diaphragm. Its presence, however, lends weight to the clinical impression when primary carcinoma of the liver is suspected in a patient.

The extremely poor prognosis in most instances of this disease may be partially accounted for by the fact that the insidious onset causes most patients to seek medical aid only after the disease is far advanced. This factor and the very nature of the disease itself have served to engender an attitude of defeatism in most physicians once the diagnosis has been made. In most instances the disease is not even suspected prior to autopsy. Behrend and Harberg[34] believe that the prognosis should not be looked upon as entirely hopeless; and they state that if resection is done whenever possible, modern surgical technique should prolong the lives of patients in certain instances. Reports indicate that other clinicians share this opinion.[7,22]

LABORATORY DATA

The laboratory findings in most reported series have not been of much aid in differential diagnosis of primary liver carcinoma, since they are relatively nonspecific, and since they may be seen in numerous other disease processes. The most consistently abnormal laboratory tests are those of liver function.

TABLE II. SUMMARY OF STATISTICAL DATA OBTAINED FROM REVIEW OF PUBLISHED CASES OF PRIMARY CARCINOMA OF THE LIVER

AUTHORS	NUMBER OF CASES	NUMBER AUTOPSIES	PERCENTAGE	NUMBER HEPATOMA	NUMBER CHOLANGIOMA	MIXED TYPE	CIRRHOSIS (%)
Schupbach and Chappell	14	797	1.76	7	2	5	57
Hoyne and Kernohan	31	16,303	0.199	20	11		54.8
Webb (Negroes)	12	1,817	0.66	11	1		100
Galluzzi, Weingarten, Zelling, Regan, and Doerner	19	2,014	1.06	16	3		
Blatchford	16	3,509	0.45	11	5		18.7
Sanford	4 biopsies 34 autopsies	9,988	0.34	35	3		52.6
Strong, Pitts, and McPhee	55 12 reduplications		0.56	41	14		87.2
Holley and Pierson	5	500	1.00				
Spatt and Grayzell	17	4,731	0.23	10	5	2	78
Lemmer	15 3 biopsies	5,228	0.28	11	6	1	55.5
McNamara, Benner, and Baker	34	5,400	0.629	25	7	2	73.5
Newman	8	8,200	0.097	8			
Jaffe		2,091					90
Loesch	14	3,000	0.464	12	2		91
Torland	10	6,000	0.166				
D'Aunoy, Ogden, and Halpert	23	6,050	0.38	16	7		

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Abel and Levy	16	4,400	0.363				
Gustafson	62	24,400	0.257	13	8		
Reports from Asia and Africa	416	39,701	1.05				
Steiner (in children)	77			52	3	22	
Charache	808	159,762	0.506				
Charache	317	16 reduplications					
Wilbur, Wood, and Willett	40	11,045	0.444	98%	8%		
Warvi	25						46
Quinland and Cuff	4	813	0.49	3	1		50
Pomeranz	3						
Behrend and Harberg	10			6			10
Goldenberg	27	8,131 1,780 surgery	0.33		67%	18	
Mass. Gen. Hosp. Path. Cases	1						
Smith	25	4,044	0.56	19	6		39
Carnahan	11	3,324	0.33				
Tomlinson and Wolff	7						
Cunningham	14	2,723	0.51				
Lynch	8			7	1		100
Rosenberg and Ochsner	55			29	13	5	70.9
Total	2,233						

TABLE III. SYMPTOMS AND SIGNS NOTED IN THE 12 CASES OF PRIMARY CARCINOMA OF THE LIVER DESCRIBED IN THIS REPORT

	ABDOMINAL PAIN	WEIGHT LOSS (LB.)	NAUSEA AND VOMITING	PALPABLE ABDOMINAL MASS	ASCITES	TEMPERATURE ELEVATION	JAUNDICE	ELEVATED RIGHT HEMIDIAPHRAGM	DILATED ABDOMINAL VEINS	DILATED LEG VEINS	PEDAL EDEMA	PALPABLE NODES
Case 1 (W.J.)	Left upper quadrant and epigastric	20	—	±	+	Low grade	—	—	—	—	—	—
Case 2 (G.M.L.)	Right upper quadrant	50	+	Nodular	—	Low grade	—	+	—	—	—	Supraclavicular
Case 3 (S.D.)	Mid-epigastric	40	+	+	+	Low grade	+ Mild	+	—	—	—	—
Case 4 (C.P.)	Right upper quadrant and epigastric	30	—	+	—	Low grade	—	+	—	—	—	—
Case 5 (W.O.)	Epigastric and right paraumbilical	Amount unknown	—	+	+	Low grade	+ Moderate	—	—	—	+	—
Case 6 (J.U.)	Right and left upper quadrant	13	+	+	+	Low grade	—	—	+	—	—	—
Case 7 (H.R.)	Epigastric radiating to right shoulder	20	—	+	—	Low grade	+ Mild	—	+	—	—	—
Case 8 (J.R.)	Right and left upper quadrant	Moderate undetermined amount	+	+ Nodular	+	Low grade	—	—	—	—	—	Supraclavicular
Case 9 (V.B.)	Epigastric	20	—	+	—	Low grade	±	—	—	+	—	—
Case 10 (E.H.)	Right and left upper quadrant	Amount unknown	—	+ Nodular	+	Low grade	+ Moderate	—	+	—	—	—
Case 11 (S.B.)	Right upper quadrant	Moderate undetermined amount	+	+ Nodular	+	Low grade	+ Mild	—	—	—	—	Inguinal
Case 12 (B.B.)	Right and left upper quadrant	18	—	+	+	Low grade	—	—	+	+	+	Axillary

+ Present. − Absent. ± Equivocal.

Varying degrees of abnormality of cephalin-cholesterol flocculation test, serum bilirubin, total serum proteins and albumin and globulin fractions, bromsulfalein retention, and alkaline phosphatase serve to confirm the clinical impression of hepatic cell damage and liver dysfunction.[40]

If anemia is present, it is usually mild or moderate. Leukocytosis is variable, and leukocyte counts ranging from 2,800 to 44,000 per cubic milliliter have been noted. Usually there is no change in the differential blood count, unless intercurrent infection supervenes. Elevation of the erythrocyte sedimentation rate has been noted in most reported cases. Some observers report it elevated in all cases studied.

REPORT OF TWELVE NEW CASES

In 715 consecutive autopsies performed at Tuskegee Veterans Administration Hospital on Negro males between 1948 and 1952, 8 cases of primary carcinoma of the liver were found. This is an autopsy rate of 1.11 per cent. Four additional cases were diagnosed by liver biopsy rather than by autopsy during this period. If these cases are added to the autopsy cases, the rate or relative frequency of the disease at this institution in autopsied patients becomes 1.67 per cent. Of the 4 patients in whom the diagnosis was determined by liver biopsy alone, 3 were explored surgically; and of these one was operated at another hospital prior to admission. In the other patient in this group, diagnosis was established by needle puncture biopsy of the liver. Ante-mortem diagnosis was correctly made by needle biopsy of the liver in 6 of the patients who came to autopsy. Thus the correct diagnosis was suspected prior to death in 10 of the 12 patients, although the diagnosis of primary carcinoma of the liver was the initial clinical impression in only 2 instances (see Table II).

Of our patients, 3 were in the fourth, 6 in the sixth, and 3 in the seventh decades. Their occupations varied, but unskilled labor predominated. All were in the "low class" bracket economically and socially. All of our patients were Negro, but there was considerable variation in the degree to which each approximated typical racial characteristics with reference to skin color, texture of hair, and general facial features. None were typical of the so-called "full-blooded" Negro of Africa. Skin color, facial contour, and texture of hair of one patient more strongly resembled those of the Caucasian race.

The symptoms noted in our 12 patients were similar to those reported in other similar series of cases in which this diagnosis was made (see Table III). All complained of abdominal pain, located in the epigastrium or the right and/or left upper quadrant of the abdomen. Weight loss was noted in 10 patients. Half of our 12 patients experienced vomiting and constipation. Loose stools were noted on various occasions by 2 patients. Vague indigestion was reported by 3 of the group. Two patients were able to palpate an abdominal mass prior to hospitalization. Other complaints included fever, excessive flatulence, abdominal distention, night sweats, dyspnea, headaches, and edema of the lower extremities. Lower extremity edema occurred in 2 of the cirrhotic patients, and most probably was the result of portal obstruction incident to this disease.

The physical signs exhibited by our patients, as in other similar series, indicated the presence of hepatocellular damage, intrahepatic obstruction, and

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TABLE IV. SUMMARY OF LABORATORY DATA OBTAINED IN THE 12 CASES OF PRIMARY CARCINOMA OF THE LIVER REPORTED IN THIS PAPER

	RBC MILLIONS/ML.^{3}	WBC THOUSANDS/ML.^{3}	HEMOGLOBIN (GM. %)	SERUM PROTEINS (GM. %)			SED. RATE MM./HR. (WINTROBE)	BUN (MG. %)	SERUM BILIRUBIN (MG. %)	CEPHALIN FLOCCULATION (48 HR.)	BSP RETENTION (45 MIN.)	ALKALINE PHOSPHATASE (BODANSKY UNITS)	PROTHROMBIN TIME (QUICK SEC.)		S.T.S	
				TOTAL	ALB.	GLOB.							PATIENT	CONTROL	KAHN	WASSERMANN
Case 1 (W.J.)	4.99	28.6	12.2	0	0	0	0	0	0	0	0	0	0	0	—	—
Case 2 (G.M.L.)	3.50	6.15	12.5	0	0	0	20	0	1.4	0	0	0	0	0	+	25%
Case 3 (S.D.)	3.19	10.0	13	5	3	1.9	22	0	3.2	2+	0	0	0	0	—	—
Case 4 (C.P.)	3.64	8.9 4.2	9.5	10.3 7.3	7.7 5.4	2.6 1.9	28	19	0.5	4+	5	6.7	18	12	—	—
Case 5 (W.O.)	3.50	7.8	13	8.7	6.1	2.6	20	0	2.2 8.0	4+	10	14	18	13	—	—
Case 6 (J.U.)	4.87	3.95	13.5	6.8	5.1	1.7	21	0	2.8	2+	15	9.9	21	15	4+	4+
Case 7 (H.R.)	5.86	10.1	17	7.9	5.5	2.4	4	0	3.6	3+	5	12.4	16	13	—	—
Case 8 (J.R.)	3.71	7.15	10.5	9.0	7.5	1.5	17	* 152	0	0	0	0	0	0	—	—
Case 9 (V.B.)	5.2 4.0	6.5 5.0	14.5 10.0	0	0	0	0	16 20	1.0	—	0	0	20	13.5	—	—
Case 10 (E.H.)	4.16	17.6	13.5	7.6	4.5	3.1	38	48	7.4	0	0	6.9	0	0	+	—
Case 11 (S.B.)	4.0 4.7	7.5 8.9	12.5 11.2	5.4	3.2	2.2	29	0*	0.6	2+	0	20	22	13	—	—
Case 12 (B.B.)	4.7 4.0	7.3 19.5	12.5 10.5	6.3	4.2	2.1	23	31	1.0	2+	3	5.0	19	14	+	+

+ Positive. — Negative. 0 No Data. * Renal Metastasis Demonstrated.

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intra-abdominal malignancy. We noted hepatomegaly in 11 patients. Nodules on the liver could be palpated in 4 subjects. Ascites was eventually demonstrated in 8, but was detected on initial physical examination in only 4. Five were jaundiced, although this was only faintly detectable on inspection in 3, and only by slightly elevated serum bilirubin in 2. Low-grade temperature elevation below 102° F. was occasionally noted in all of our patients. Palpable supraclavicular nodes were noted in 2 patients, axillary lymphadenopathy in 1, and inguinal lymphadenopathy in 1. Dilated abdominal veins, which were seen in 2 of the patients with cirrhotic involvement, further supported the evidence of portal obstruction in them. Dilated leg veins and protruding hemorrhoids were also observed in 1 of these 2. Since only 3 patients were found to have cirrhosis, the ascites in 8 and the jaundice in 5 seem to suggest that these abnormalities in some of these cases may be attributed to changes resulting from tumor proliferation or other factors. Vascular spiders (angiomata) were not observed in our group of patients. This sign seems to be observed infrequently in Negro patients with other signs of portal obstruction. Elevation of the right hemidiaphragm was noted on x-ray in 3 of our group.

The laboratory data tended to parallel those reported in many similar cases in the literature (see Table IV). Liver function tests were most consistently abnormal, as evidenced by the fact that all our patients tested had abnormal liver function studies in varying degrees. Of 5 patients tested for bromsulfalein retention, all had mild to moderate retention of the dye 45 minutes after injection. The prothrombin time was slightly prolonged in each of 7 patients. All of 7 tested for alkaline phosphatase showed mild to moderate elevations not exceeding 20 Bodansky units. Abnormal cephalin flocculation of 2+ to 4+ was noted in 7 of the 9 patients tested. Mild to moderate elevation of the serum bilirubin was noted in 5 of 10 patients on whom the test was done.

Varying degrees of elevation of the erythrocyte sedimentation rate was seen in 10 of the 12 patients, while 4 had a mild to moderate leukocytosis of 10,000 to 19,000. In one other instance, however, a white cell count of 28,000 per cubic milliliter was reported, with 90 per cent polymorphonuclear neutrophils (Case 1). A mild anemia was present in 5, with erythrocyte counts ranging from 3.1 million to 3.7 million, while the hemoglobin ranged from 9.5 to 12 Gm. Other laboratory data included slight to moderate elevation of the blood urea nitrogen in 3 of 5 patients tested, low total proteins without reversal of albumin-globulin ratio in 2 of 9 patients tested, and positive serologic test for syphilis in 4 of 12 patients tested. Unfortunately, for various reasons, completely satisfactory laboratory data were not obtained in all our cases.

In our group of 12 cases, there were 10 of hepatoma and 2 of cholangioma (see Table II). Careful microscopic study of the tissue specimen by 3 pathologists revealed cirrhosis in only 3 instances. The reason for this relative paucity is unknown, but it is noted that this figure of 25 per cent closely approximates that of Blatchford's 14 cases, in which 21 per cent cirrhosis was found. In our cases, however, if only the autopsy cases are considered (with respect to the presence of cirrhosis), this percentage increases to 37.5, which is still below that of most other reports. Perhaps the relatively good nutritional history in most of our patients (in terms of current standards) accounts for this difference.

Extrahepatic metastases were noted in 9 of our patients. These involved predominantly the mediastinal lymph nodes, lungs, and periaortic nodes. Other metastatic sites included kidney, gall bladder, pancreas, spleen, serosa of stomach,

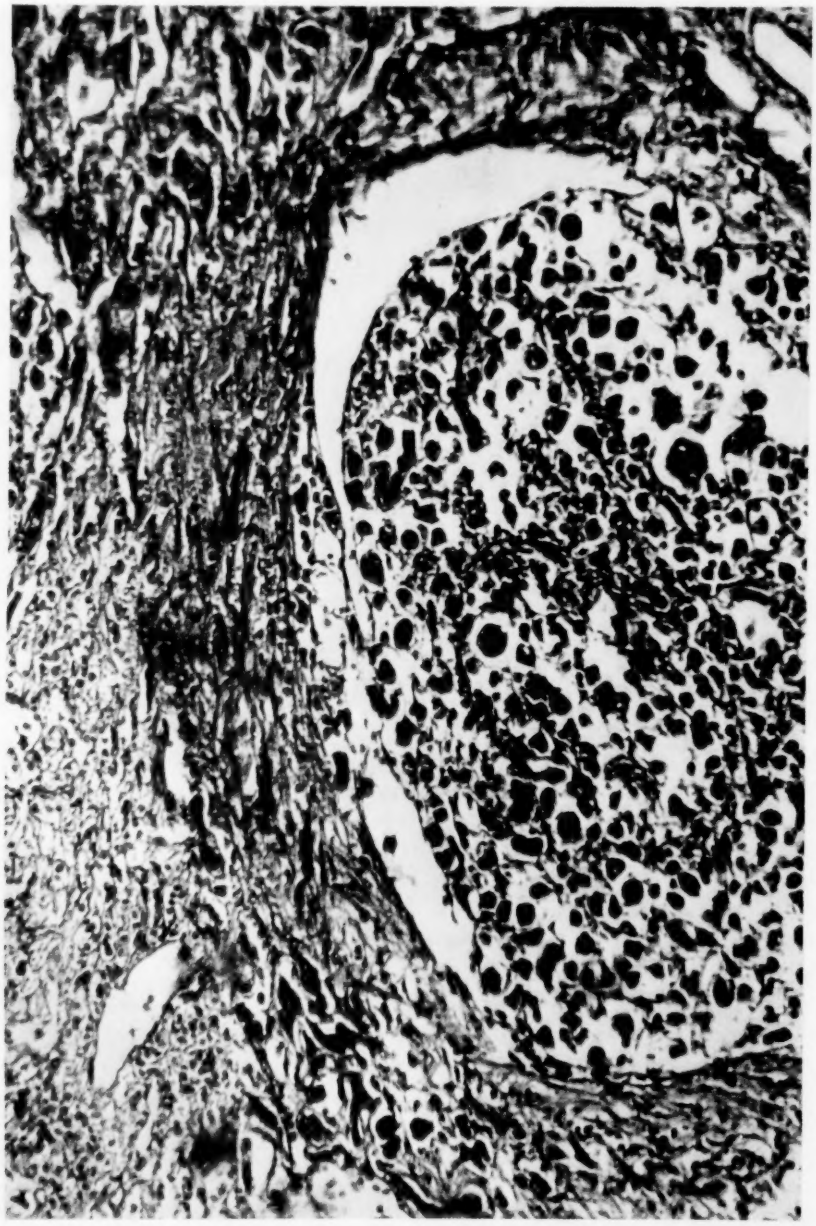

Fig. 1.—Photomicrograph of hepatoma metastasis in blood sinus of liver; hence the multicentric development of the tumor in the liver. The tumor cells are identical with those of the primary tumor. Hepatic columns are seen at left. (Low-power magnification.)

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and urinary bladder. (Although splenomegaly was not detected on physical examination in any of our patients, it was found at autopsy in 4, 2 of whom had histologic evidence of cirrhosis. The largest spleen weighed 250 grams [Case 12]). Metastatic involvement of these organs with tumor tissue was grossly evident; and in one instance the liver, serosa of the stomach, omentum, pancreas, and spleen were intimately adhered so as to form a single mass.

RACE AND ENVIRONMENT IN PATHOGENESIS OF THE DISEASE

The question of the role of racial susceptibility and environmental factors in the pathogenesis of this disease has not been settled. Accumulated clinical data suggest that pigmented racial groups are unusually susceptible to primary carcinoma of the liver; but other reports indicate that environmental factors rather than race may be primarily responsible. Berman[13] has reported a high rate of occurrence of primary liver carcinoma in the Bantu natives of South Africa. He also called attention to reported high rates among the Javanese, Japanese, Chinese, and Filipinos. Since, according to Berman, this disease has been found 40 times more frequently in pigmented than in nonpigmented racial groups, regardless of geographic location, this investigator has postulated a racial susceptibility to the disease. However, if pigmentation per se is of primary importance, it is difficult to explain the wide variation of autopsy rates in different pigmented groups. The autopsy rate for the disease in the Javanese, as stated by Berman, is 1.3 per cent; but the rate in British West Indians is recorded as 0.32 per cent. More recently, Berman[42] has stated that a common genetic factor as a probable cause of primary liver carcinoma among groups so widely scattered geographically seems less likely than does the factor of environment.

Certain case reports also minimize the racial factor. Such a report is that of Galluzzi and others.[40] In their series of 19 cases of primary hepatic carcinoma in patients at the United States Public Health Service Hospital at Staten Island, New York, there were 3 Filipinos, 1 Chinese, and 15 Caucasians. The size of the series and other factors, of course, limit the statistical significance of the results.

The relative frequency of occurrence of primary carcinoma of the liver in Negro patients at our Institution possibly lends some superficial support to the racial susceptibility theory. Since more specific detailed data relative to this aspect of the subject are not available, the question of racial susceptibility cannot be clearly delineated.

In our group of patients, the factors of low economic and social status stand out with considerable prominence. This seems to prevail in a majority of the pigmented racial groups reported in the literature on this subject, although there are recorded cases from the upper stratum of society also. This suggests to us, as it has to others, that there may be other undiscovered factors, nutritional or otherwise, related in some way, to the mode of living, which may be more important than pigmentation per se in influencing the development of primary carcinoma of the liver in certain groups. Perhaps closer correlation of more specific factors in the mode of living which are common to all such groups would

serve to illuminate the problem further. Such a study presents many difficulties; and this possibly accounts for the fact that satisfactory data of this type are not available in the literature to date.

SUMMARY

Twelve additional cases of primary carcinoma of the liver are added to the 2,205 cases found in a review of the literature. The 16 reduplications of Charache as recorded by Warvi were excluded from this total. Our autopsy rate of 1.11 per cent, although in a small series, is considered possibly significant when compared to similar series.

Comparison of findings in a selected small group of patients such as ours with those of larger groups of various races, sex, age, and economic status prohibits positive valid conclusions; but it is of interest to note similarities and differences, which eventually may lead to delineation of more specific factors in the development of this disease. We believe that our cases support the impression of other investigators that the relative frequency of occurrence of primary carcinoma of the liver seems to be increasing in the United States. To be remembered, however, is the fact that the life expectancy of the general population, especially in this country, has increased considerably in recent years. Since fewer people now succumb to diseases which formerly resulted in the early death of many, this factor may have influenced the prevalence of primary liver carcinoma.

In general, our findings relative to symptoms, physical signs, laboratory data and extrahepatic metastases parallel those of other authors. The pathologic finding of cirrhosis of the liver was noted in only 3 of our 12 patients; whereas in similar small series, as well as larger ones, other reports indicate the presence of cirrhosis in a considerably higher percentage of patients with primary carcinoma of the liver. The reason for this difference is not known. Perhaps the explanation lies in the fact that the nutritional background was good in all but 2 of our patients, and a history of excessive consumption of alcohol was found in only 4.

In our 12 cases, no definite predisposing factors such as race, occupation, nutrition, alcoholism, occupation, and parasitic infestation can be cited as of definite etiologic significance in the development of this disease. Although our cases may be considered by some to lend support to the theory of racial susceptibility, satisfactory data with reference to this factor are lacking. We believe that other unknown factors related to economic and social status or the mode of living may be of special significance in the pathogenesis of primary carcinoma of the liver.

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THE EFFECTS OF AN ANALEPTIC (RITALIN), AN ATARAXIC (RESERPINE), AND A PLACEBO IN SENILE STATES

ARTHUR H. DUBE, M.D., CHARLES K. OSGOOD, M.D., AND HERBERT NOTKIN, M.D.

SYRACUSE, N. Y.

From the Departments of Medicine and Public Health, State University of New York Medical Center, Syracuse, N. Y.

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THE Edward S. Van Duyn County Memorial Hospital is devoted to the care of the chronically ill. Its population includes a large number of senile patients. These patients have as a common denominator mental and/or physical deterioration resulting from their underlying chronic illness or infirmity. The mental deterioration embraces a wide range of change varying from mild confusion to disorientation. Patients with overt psychoses (hallucinations, major delusions, mania or severe depression) are transferred from the institution and are not included in the senile group. It was noted as an incidental finding that as attempts were made to improve the outlook and performance of these senile patients, an increasing amount of tranquilizing (i.e., reserpine) or analeptic drugs (i.e., amphetamine) was being used. In several patients our observations suggested that these drugs had therapeutic merit. These observations and the encouraging reports of other investigators[1,2] led us to plan a controlled study in an effort to determine whether the apparent merit was real.

In a senile population there are slow fluctuations of spontaneous improvement and decline which may falsely influence any clinical study. To minimize these variations our study was designed to test these drugs over a reasonably long period of time without knowledge of the observer as to the identity of the medications until the completion of the study. The first part of the study was designed to evaluate individual responses to the various drugs, and the second part deals with the use of the drugs in combination.

METHOD

Twenty patients were selected to evaluate reserpine, a placebo, and a new analeptic preparation, methyl-phenidylacetate (Ritalin). The latter drug has been reported valuable in improving senile behavior by Ferguson and Fun-

Ritalin, Reserpine, and Placebo tablets kindly supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

derburk.[2] A supply of identical appearing tablets was labeled "A," "B," and "C." The key to the identity of these agents was unknown to any of the physicians or nurses carrying out the study. It was not released until the complete study had been tabulated. Our patient group was limited to men. Their average was 72 years, with a range of 51 to 90 years. They had a variety of illnesses with mental and/or physical deterioration resulting in senility of diverse degree. After a four-week control period, medication was started, assigning the drugs to the patients on a random basis. The dosage schedule consisted of one tablet given orally four times daily, swallowed by the patient under the observation of the medication nurse. The dose of reserpine was 0.25 mg. per tablet and of Ritalin 10 mg. per tablet. The medication was continued for four weeks and then switched without a rest period, the changes being unknown to the patients. Following a suitable rest period, the drugs were given in combination. The medications were not identified until both phases of the study had been completed.

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The results were tabulated and an over-all clinical impression was determined, based on whether there was improvement, no change, or worsening during the study period. To establish the degree of change, an arbitrary point scale was assigned. The amount of improvement or worsening was graded on a scale of plus or minus 0 to 3 for each patient. Improvement was given a plus value and worsening a negative value. The total net result for each drug was then tabulated.

EVALUATION

A baseline evaluation was made after the control period, and subsequent weekly evaluations were made by the nursing, medical, and physiotherapy staffs. Independent weekly notes were recorded by the nursing and physiotherapy staffs, and the weekly grading was decided after a joint conference of the three groups. Progress was judged in these general categories: "physical state," "mental state," and "progress in rehabilitation." In evaluating the physical state, general muscle strength, physical condition, and bladder-bowel continence were considered. The mental state was based on orientation, alertness, and general interest. The rehabilitation progress was based on ability to eat, stand or walk, alone or with assistance, plus the patient's interest in the rehabilitation procedures. The grading was based on a scale of 0-poor, 1-fair, 2-good, 3-excellent, and 4-optimum.

The over-all evaluation made at the end of the study compared each period with the one preceding it and with the original control period, the latter being the major point of comparison. At the end of each four-week period, albumin and sugar in urine, hemoglobin and white blood count, weight and blood pressure were recorded. All patients were kept on the standard hospital diet and were given a daily multiple vitamin preparation which had been started one month before the study was instituted. All other medications that had been used for various chronic disorders were continued. The initial test medication was assigned on a random basis and the following sequence was used.

	First	*Second*	*Third*
Group 1	Ritalin	Placebo	Reserpine
Group 2	Reserpine	Ritalin	Placebo
Group 3	Placebo	Reserpine	Ritalin

Although Ritalin is rapidly excreted, there is a delay in excretion of reserpine.[3] Since there were no rest periods between drugs, some degree of overlapping was anticipated. A rest period was intentionally avoided in order to create the impression that all patients were receiving the same medication throughout the entire study.

RESULTS

A complete summary of all the patients and the results of the three agents are given in Table III. There were no significant toxic effects noted, and the urine, blood counts, and weights remained reasonably constant throughout the study. We could detect no appreciable effects in blood pressure with either Ritalin or reserpine as compared with the placebo. The over-all clinical impression indicated that Ritalin exerted a beneficial effect which was chiefly reflected in an improvement in mental status. These results are summarized in Table I.

TABLE I. THE RESULTS OF RITALIN AND RESERPINE COMPARED

	PHYSICAL	MENTAL	REHABILITATION
Ritalin	4 I 1 W 15 NC	11 I 0 W 9 NC	6 I 2 W 12 NC
Reserpine	2 I 2 W 16 NC	6 I 2 W 12 NC	1 I 2 W 17 NC
Placebo	2 I 2 W 16 NC	6 I 4 W 10 NC	2 I 1 W 17 NC

I = Improved. W = Worse. NC = No Change.

Since there were frequent variations in the degree of change, a quantitative estimate of pretreatment and posttreatment status, based on the following point scale, was designated:

NC	= (No change)	0
SI	= (Slight improvement)	+1
MoI	= (Moderate improvement)	+2
MI	= (Marked improvement)	+3

Negative results were subtracted as follows:

SW	= (Slightly worse)	−1
MoW	= (Moderately worse)	−2
MW	= (Markedly worse)	−3

The total net result in all three categories—physical, mental, and rehabilitation—was determined and is recorded in Table II.

TABLE II. THE NET EFFECT OF TREATMENT WITH RITALIN AND RESERPINE

	IMPROVEMENT	WORSENING	NET
Ritalin	+37	− 5	+32
Reserpine	+12	− 7	+ 5
Placebo	+13	−11	+ 2

In the quantitative estimate, the beneficial effects of Ritalin paralleled the previously recorded over-all clinical impression, but the degree of improvement as compared with reserpine and placebo was far more striking. At the dosage level which we employed, reserpine exerted no appreciable effect, either for improvement or worsening, as compared with the placebo. In one patient, Ritalin had an adverse effect with irritability as the major manifestation. Reserpine frequently caused marked drowsiness. In three patients with Parkinson's disease, Ritalin produced improvement with less tremor. In one patient who had frequent oculogyric crises while on routine treatment for Parkinson's disease, the crises were completely relieved during Ritalin therapy. Although we had anticipated overlapping due to the delayed excretion of reserpine, we were unable to detect any at these dosage levels. Further studies of Ritalin at varying dosage levels in senile states and perhaps in Parkinson's disease might be rewarding.

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RITALIN AND RESERPINE IN COMBINATION

It has been reported that combinations of Ritalin and Reserpine are even more beneficial in treating senile behavior than either acting alone.[2] To study this point further, we have conducted a controlled study using these drugs in combination.

Nineteen of our original 20 patients were chosen (one had died of a myocardial infarction during the rest period between studies). Two senile men were added to the original patients, bringing the total group to 21.

During the study, the number of patients decreased to 18. Two patients (W.D. and E.B.) died of natural causes during the treatment period, and one patient (R.W.) became so irritable while on Ritalin plus the placebo that he had to be dropped from the study. This same patient had been extremely irritable while on Ritalin previously. These three patients are not included in the analysis of the results, but are listed at the end of Table VI, a complete tabulation of all the patients. The results then are based on 18 patients, 16 of whom had previously been on Ritalin, reserpine, or a placebo, each used separately.

METHOD

Two weeks after completion of the first phase of the study, an interval during which no medication of this type was used, a study of these drugs in

TABLE III. THE DETAILS OF THERAPY WITH RITALIN, RESERPINE, AND A PLACEBO, EACH USED ALONE

	DRUGS	PHYSICAL	MENTAL	REHABILITATION	REMARKS
1. M. H. 82—Group I ADM. 10/29/53 DX. (1) CVA rt. hemiplegia (2) Auricular fibrillation (3) Parkinson's disease Rx (1) Digitalis 0.1 Gm./day	Ritalin	NC	NC	NC	Less shaky
	Reserpine	NC	NC	NC	
	Placebo	NC	NC	NC	
2. C. R. 85—Group I ADM. 1/31/55 DX. (1) Posttraumatic amputation rt. thigh with postoperative mental regression Rx (1) Urotropin 1 tab. t.i.d. (2) Aspirin 0.3 Gm. t.i.d.	Ritalin	NC	NC	NC	
	Reserpine	SW	MW	NC	
	Placebo	SW	MW	NC	Paranoid this period
3. D. K. 60—Group I ADM. 1/29/52 DX. (1) Chronic alcoholism with bilateral posttraumatic subdural hematoma, 1952 (2) Rheumatic heart disease with aortic insufficiency (3) Acne rosacea Rx None	Ritalin	SI	MI	MoI	
	Reserpine	NC	SI	NC	
	Placebo	NC	MoW	NC	
4. E. D. 58—Group I ADM. 12/28/53 DX. (1) Arrested syphilis (2) Aortic insufficiency (3) Left hemiparesis (4) Postphlebitic legs Rx None	Ritalin	SI	SI	SI	
	Reserpine	MoW	NC	NC	
	Placebo	NC	NC	NC	
5. J. P. 55—Group I ADM. 12/24/53 DX. (1) Parkinson's disease (2) Oculogyric crisis Rx (1) Hyoscine 0.4 mg. t.i.d. (2) Artane 2 mg. t.i.d.	Ritalin	MoI	NC	MoI	Parkinson's improved and no oculogyric crisis
	Reserpine	NC	NC	SW	Less agreeable; frequent oculogyric crisis
	Placebo	SW	NC	SW	Frequent oculogyric crisis

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6. W. D. 59—Group I ADM. 7/22/53 DX. (1) Rt. parietal oligodendroglioma removed in 1951 (2) Residual left hemiplegia (3) Grand mal epilepsy Rx (1) Phenobarb. 32 mg. b.i.d. (2) Dilantin 0.1 Gm. b.i.d.	Ritalin	NC	MoI	NC	One small epileptic seizure
	Reserpine	NC	NC	NC	
	Placebo	NC	MoW	NC	
7. R. R. 71—Group I ADM. 6/24/55 DX. (1) Cerebral vascular accident, 1953 (2) Rt. hemiplegia and aphasia (3) Arteriosclerotic heart disease with heart failure Rx (1) Digitalis 0.1 Gm./day	Ritalin	MoW	NC	MoW	Control weight 119; developed pneumonia
	Reserpine	MoI	SI	NC	Recovering from pneumonia
	Placebo	NC	SI	NC	Recovered from pneumonia
8. W. G. 77—Group II ADM. 9/21/54 DX. (1) Cancer of colon, 1949, with resection and colostomy (2) Generalized arteriosclerosis with cerebral changes Rx None	Ritalin	NC	NC	NC	
	Reserpine	NC	NC	NC	Very drowsy
	Placebo	NC	SI	NC	
9. J. S. 77—Group II ADM. 2/29/51 DX. (1) Paget's disease 40 years (2) Anemia (3) Arteriosclerotic heart disease with heart failure Rx (1) Digitalis 0.1 Gm./day (2) NH_4Cl 0.6 Gm./day (3) Aspirin 0.6 Gm./day	Ritalin	NC	SI	NC	
	Reserpine	NC	NC	NC	Sleepy
	Placebo	NC	NC	NC	
10. G. F. 74—Group II ADM. 6/23/48 DX. (1) Cerebral vascular accident, 1948 (2) Left hemiplegia (3) Cataracts Rx None	Ritalin	NC	MoI	NC	
	Reserpine	NC	MoI	NC	"Feels better all over"
	Placebo	NC	NC	NC	More drowsy

NC = No change.
SI = Slight improvement.
MoI = Moderate improvement.
MI = Marked improvement.
DX = Diagnosis.

CVA = Cerebral vascular accident.
SW = Slightly worse.
MoW = Moderately worse.
MW = Markedly worse.

TABLE III—CONT'D

	DRUGS	PHYSICAL	MENTAL	REHABILITATION	REMARKS
11. E. B. 90—Group II ADM. 11/16/54 DX. (1) Arteriosclerotic heart disease with heart failure (2) Chronic pyelonephritis Rx (1) Digitalis 0.1 Gm./day	Ritalin	NC	SI	NC	
	Reserpine	NC	SI	NC	Sleepy
	Placebo	NC	MoI	NC	Mild pneumonia first week of this period
12. B. S. 89—Group II ADM. 11/3/52 DX. (1) Cerebral vascular accident, 1952 (2) Right hemiplegia (3) Generalized arteriosclerosis with cerebral changes Rx None	Ritalin	NC	MoI	NC	
	Reserpine	NC	NC	NC	
	Placebo	NC	MoW	NC	
13. A. K. 60—Group II ADM. 3/4/54 DX. (1) Parkinson's disease (2) Generalized arteriosclerosis with cerebral changes Rx (1) Artane 2 mg. b.i.d.	Ritalin	NC	MoI	SI	Steadier, walking better
	Reserpine	SI	SI	MoI	
	Placebo	NC	NC	NC	
14. H. H. 78—Group II ADM. 9/15/55 DX. (1) Cerebral arteriosclerosis with senile changes since 1953 (2) Cerebral vascular accident, 1955, with right hemiplegia Rx None	Ritalin	NC	NC	NC	
	Reserpine	NC	NC	NC	
	Placebo	SI	MoI	MoI	
15. W. C. 72—Group III ADM. 7/5/55 DX. (1) Generalized arteriosclerosis with cerebral changes Rx None	Ritalin	NC	NC	NC	
	Reserpine	NC	NC	NC	
	Placebo	NC	NC	NC	

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16. P. C. 72—Group III ADM. 11/21/54 DX. (1) Cerebral vascular accident in 1953 (2) Left hemiplegia Rx None	Ritalin	NC	MoI	SI	
	Reserpine	NC	SI	NC	
	Placebo	NC	NC	NC	
17. G. S. 85—Group III ADM. 10/27/54 DX. (1) Arteriosclerotic heart disease with heart failure (2) Benign prostatic hypertrophy with urinary obstruction Rx (1) Digitalis 0.1 Gm./day (2) Thiomerin 2 c.c./wk.	Ritalin	MI	MI	MoI	
	Reserpine	NC	SW	NC	Sleepy
	Placebo	NC	SI	NC	
18. F. M. 70—Group III ADM. 11/10/53 DX. (1) Cerebral vascular accident in 1953 (2) Left hemiplegia Rx None	Ritalin	NC	MoI	NC	
	Reserpine	NC	NC	NC	
	Placebo	NC	NC	NC	
19. L. T. 70—Group III ADM. 6/1/50 DX. (1) Congenital spastic paralysis (2) Convulsive disorder Rx (1) Phenobarb. 15 mg. t.i.d.	Ritalin	NC	NC	NC	
	Reserpine	NC	NC	NC	
	Placebo	NC	NC	NC	
20. R. W. 51—Group III ADM. 3/24/53 DX. (1) Cerebral vascular accident, 1950, with rt. hemiplegia (2) Generalized arteriosclerosis (3) Convulsive disorder Rx (1) Dilantin 0.1 Gm. t.i.d.	Ritalin	NC	NC	SW	Very irritable
	Reserpine	NC	NC	NC	
	Placebo	SI	SI	SI	

combination was begun. The tablets were again labeled "A," "B," and "C," but the labels had been switched, so that they were no longer the same as in the initial study. The key was not released until the end of the study. The 18 patients were all males with varying degrees of senility. The schedule consisted of one tablet of each designated combination at the same dosage level of Ritalin and reserpine as before, four times daily. The initial dosage schedule was assigned at random and is given as follows:

	First	*Second*	*Third*
Group 1	Placebo and Reserpine	Ritalin and Placebo	Reserpine and Ritalin
Group 2	Reserpine and Ritalin	Placebo and Reserpine	Ritalin and Placebo
Group 3	Ritalin and Placebo	Reserpine and Ritalin	Placebo and Reserpine

The treatment periods were each four weeks with no rest periods between combinations. The results were evaluated on the same basis as previously.

RESULTS

A complete summary of all the patients and their responses to the drug combinations is given in Table VI. No significant toxic effects or consistent changes in blood counts, urines, blood pressures, or weights were noted. An initial over-all clinical impression is recorded in Table IV.

TABLE IV. THE RESULTS OF COMBINED THERAPY

	PHYSICAL	MENTAL	REHABILITATION
Placebo and Reserpine	1 I 3 W 14 NC	3 I 3 W 12 NC	2 I 3 W 13 NC
Reserpine and Ritalin	1 I 3 W 14 NC	3 I 2 W 13 NC	2 I 3 W 13 NC
Ritalin and Placebo	7 I 1 W 10 NC	12 I 0 W 6 NC	8 I 0 W 10 NC

I = Improved. W = Worse. NC = No change.

The initial evaluation indicated that Ritalin plus placebo exerted significantly beneficial effects in all spheres—physical, mental, and rehabilitation—whereas reserpine in combination either with Ritalin or with a placebo, had no such effect.

The net effect for each combination was tabulated in Table V, using the same scale as previously employed (cf. Table II).

TABLE V. THE NET EFFECT OF COMBINED TREATMENT

	IMPROVEMENT	WORSENING	NET
Placebo and Reserpine	+ 5	−21	−16
Reserpine and Ritalin	+ 6	−15	− 9
Ritalin and Placebo	+48	0	+48

The results coincided with the initial clinical impression, namely marked improvement while on Ritalin and placebo, but no appreciable favorable changes when reserpine was combined with either placebo or Ritalin. The most active preparation seems again to be Ritalin whereas reserpine has no appreciable effects. When reserpine is used in combination with Ritalin, it seems to nullify the beneficial effects observed with Ritalin alone.

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CONCLUSIONS

1. In 20 senile patients treated over a three-month period with reserpine, Ritalin, and a placebo, Ritalin exerted a beneficial effect, especially in the mental status, in 11 of these patients. Three patients with Parkinson's disease had marked improvement in their tremor and general physical state while on Ritalin.
2. On the basis of a quantitative estimate using an arbitrary point system, Ritalin caused definite over-all improvement, whereas reserpine and the placebo had no appreciable effects.
3. Ritalin has therapeutic value in improving the mental and physical changes associated with senility in some patients. Further studies at varying dosage levels would appear to be useful.
4. Ritalin combined with a placebo exerted beneficial effects in the mental state of 12 of 18 senile patients studied. Improvement was also noted in the physical state and in rehabilitation progress in slightly less than half of this group.
5. Combinations of reserpine with either placebo or Ritalin at the dosage levels used exerted no discernible beneficial effects.
6. The apparent beneficial effects of Ritalin seemed to be offset by the addition of reserpine.

We wish to thank Dr. Richard H. Lyons for his help and suggestions during this study.

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(Table VI on pages 230-234.)

TABLE VI THE DETAILS OF THERAPY WITH RITALIN AND RESERPINE USED IN COMBINATION WITH EACH OTHER OR WITH A PLACEBO

	DRUGS	PHYSICAL	MENTAL	REHABILITATION	REMARKS
1. M. H. 82—Group I ADM. 10/29/53 DX. (1) CVA rt. hemiplegia (2) Auricular fibrillation (3) Parkinson's disease Rx (1) Digitalis 0.1 Gm./day	Placebo and Reserpine	NC	NC	NC	Perhaps less shaky
	Reserpine and Ritalin	NC	NC	SW	Very shaky; not walking as well
	Ritalin and Placebo	MoI	SI	MoI	Much less tremor; walking better
2. C. R. 85—Group I ADM. 1/31/55 DX. (1) Posttraumatic amputation rt. thigh with postoperative mental regression Rx (1) Urotropin 1 tab. t.i.d. (2) Aspirin 0.3 Gm. t.i.d.	Placebo and Reserpine	NC	MW	MoW	Very sleepy
	Reserpine and Ritalin	NC	SI	NC	
	Ritalin and Placebo	NC	MoI	NC	More alert and cooperative
3. D. K. 60—Group I ADM. 1/29/52 DX. (1) Chronic alcoholism with bilateral posttraumatic subdural hematoma, 1952 (2) Rheumatic heart disease with aortic insufficiency (3) Acne rosacea Rx None	Placebo and Reserpine	SI	NC	SI	
	Reserpine and Ritalin	NC	SI	NC	
	Ritalin and Placebo	NC	SI	NC	Arthritic pain in hips and ankles
4. E. D. 58—Group I ADM. 12/28/53 DX. (1) Arrested syphilis (2) Aortic insufficiency (3) Left hemiparesis (4) Postphlebitic legs Rx None	Placebo and Reserpine	MoW	NC	NC	Incontinent
	Reserpine and Ritalin	NC	NC	NC	
	Ritalin and Placebo	MoI	SI	SI	Getting out of bed unassisted
5. J. P. 55—Group I ADM. 12/24/53 DX. (1) Parkinson's disease (2) Oculogyric crisis Rx (1) Hyoscine 0.4 mg. t.i.d. (2) Artane 2 mg. t.i.d.	Placebo and Reserpine	NC	NC	NC	
	Reserpine and Ritalin	NC	NC	NC	Oculogyric crises more frequent
	Ritalin and Placebo	MI	NC	MI	No oculogyric crises Tremor and strength much improved

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6. R. R. 71—Group I ADM. 6/24/55 DX. (1) Cerebral vascular accident in 1953 (2) Rt. hemiplegia and aphasia (3) Arteriosclerotic ht. disease with heart failure Rx (1) Digitalis 0.1 Gm./day	Placebo and Reserpine	NC	NC	SI	
	Reserpine and Ritalin	SI	NC	SI	
	Ritalin and Placebo	MoI	SI	MoI	Leg brace obtained Walking much better
7. W. G. 77—Group II ADM. 9/21/54 DX. (1) Cancer of the colon, 1949, with resection and colostomy (2) Generalized arteriosclerosis with cerebral changes Rx None	Placebo and Reserpine	NC	NC	NC	Drowsy
	Reserpine and Ritalin	NC	NC	NC	
	Ritalin and Placebo	NC	NC	NC	
8. J. S. 77—Group II ADM. 2/29/51 DX. (1) Paget's disease, 40 years (2) Anemia (3) Arteriosclerotic heart disease with heart failure Rx (1) Digitalis 0.1 Gm./day (2) NH_4Cl 0.6 Gm./day (3) Aspirin 0.6 Gm./day	Placebo and Reserpine	NC	NC	NC	
	Reserpine and Ritalin	NC	NC	NC	Sleepy and indifferent
	Ritalin and Placebo	NC	MoI	NC	
9. G. F. 74—Group II ADM. 6/23/48 DX. (1) Cerebral vascular accident, 1948 (2) Left hemiplegia (3) Cataract operation Rx None	Placebo and Reserpine	NC	SI	NC	
	Reserpine and Ritalin	SW	SW	NC	
	Ritalin and Placebo	MoI	MoI	SI	Eating unassisted for the first time
10. B. S. 89—Group II ADM. 11/3/52 DX. (1) Cerebral vascular accident, 1952 (2) Right hemiplegia (3) Generalized arteriosclerosis with cerebral changes Rx None	Placebo and Reserpine	NC	NC	NC	Developed cellulitis of rt. elbow, third week
	Reserpine and Ritalin	NC	SI	NC	Recognized daughter for the first time in several years
	Ritalin and Placebo	NC	NC	NC	

NC = No change.
SI = Slight improvement.
MoI = Moderate improvement.
MI = Marked improvement.
DX = Diagnosis.
CVA = Cerebral vascular accident.
SW = Slightly worse.
MoW = Moderately worse.
MW = Markedly worse.

TABLE VI—CONT'D

	DRUGS	PHYSICAL	MENTAL	REHABILITATION	REMARKS
11. A. K. 60—Group II ADM. 3/4/54 DX. (1) Parkinson's disease (2) Generalized arteriosclerosis with cerebral changes Rx (1) Artane 2 mg. b.i.d.	Placebo and Reserpine	SW	MoW	MoW	Much more drooling; unsteady and shaky
	Reserpine and Ritalin	MoW	NC	SW	Scratching head and less shaky
	Ritalin and Placebo	SI	MoI	SI	Looks much better; less drooling and less unsteadiness
12. H. H. 78—Group II ADM. 9/15/55 DX. (1) Cerebral arteriosclerosis with senile changes since 1953 (2) Cerebral vascular accident, 1955, with right hemiplegia Rx None	Placebo and Reserpine	NC	SI	NC	More cooperative
	Reserpine and Ritalin	NC	NC	NC	
	Ritalin and Placebo	SW	NC	NC	Completely incontinent; grinding teeth
13. H. F. 84—Group III ADM. 3/15/56 DX. (1) Diabetes mellitus with neuropathy (2) Generalized arteriosclerosis with amputation left leg (3) Arteriosclerotic heart disease with auricular fibrillation and mild cardiac compensation Rx (1) Digitalis 0.1 Gm./day (2) Thiomerin 2 c.c./wk.	Placebo and Reserpine	NC	NC	NC	
	Reserpine and Ritalin	NC	NC	NC	Sleepy, "feels very dopy"
	Ritalin and Placebo	NC	MoI	NC	Much more agreeable
14. W. W. 69—Group III ADM. 2/3/56 DX. (1) Senile psychosis (2) Arteriosclerotic heart disease with congestive heart failure (3) Cataracts Rx (1) Digitalis 0.1 Gm./day	Placebo and Reserpine	NC	NC	NC	Steadily downhill
	Reserpine and Ritalin	NC	SI	NC	Steadily downhill
	Ritalin and Placebo	NC	SI	NC	Less shaky

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15. P. C. 72—Group III ADM. 11/21/54 DX. (1) Cerebral vascular accident, 1953 (2) Left hemiplegia Rx None	Placebo and Reserpine	NC	NC	NC	Not as agreeable
	Reserpine and Ritalin	NC	NC	SI	
	Ritalin and Placebo	NC	SI	SI	
16. G. S. 85—Group III ADM. 10/27/54 DX. (1) Arteriosclerotic heart disease with heart failure (2) Benign prostatic hypertrophy with urinary obstruction Rx (1) Digitalis 0.1 Gm./day (2) Thiomerin 2 c.c./wk.	Placebo and Reserpine	MW	MW	MW	Sleepy and weak
	Reserpine and Ritalin	MW	MW	MW	Sleepy, irritable
	Ritalin and Placebo	MI	MI	MI	Excellent progress
17. F. M. 70—Group III ADM. 11/10/53 DX. (1) Cerebral vascular accident, 1953 (2) Left hemiplegia	Placebo and Reserpine	NC	NC	NC	
	Reserpine and Ritalin	NC	NC	NC	Drowsy
	Ritalin and Placebo	NC	NC	NC	
18. L. T. 70—Group III ADM. 6/1/50 DX. (1) Congenital spastic paralysis (2) Convulsive disorder Rx (1) Phenobarb. 15 mg. t.i.d.	Placebo and Reserpine	NC	SI	NC	
	Reserpine and Ritalin	NC	SI	NC	
	Ritalin and Placebo	NC	NC	NC	Very irritable

TABLE VI—CONT'D

	DRUGS	PHYSICAL	MENTAL	REHABILITATION	REMARKS
Not Tabulated					
1. W. D. 59 ADM. 7/22/53 DX. (1) Rt. parietal obligodendroglioma removed in 1951 (2) Residual left hemiplegia (3) Grand mal epilepsy Rx (1) Phenobarb. 32 mg. b.i.d. (2) Dilantin 0.1 Gm. b.i.d.	Placebo and Reserpine	SI	SI	NC	
	Reserpine and Ritalin				
	Ritalin and Placebo	NC	SI	NC	Expired 4/23/56, during third week of Ritalin and placebo. Post-mortem revealed pneumonia and recurrent obligondendroglioma
2. E. B. 90 ADM. 11/16/54 DX. (1) Arteriosclerotic heart disease with heart failure (2) Chronic pyelonephritis Rx (1) Digitalis 0.1 Gm./day	Placebo and Reserpine	MoW	NC	MoW	
	Reserpine and Ritalin	NC	SI	SI	More agreeable
	Ritalin and Placebo	NC	SI	NC	Expired 5/27/56, during third week. Had developed high fever and cough. Diagnosis, pneumonitis. Post-mortem refused
3. R. W. 51 ADM. 3/24/53 DX. (1) Cerebrovascular accident, 1950, with rt. hemiplegia (2) Generalized arteriosclerosis (3) Convulsive disorder Rx (1) Dilantin 0.1 Gm. t.i.d.	Placebo and Reserpine				
	Reserpine and Ritalin				
	Ritalin and Placebo				Depressed and extremely irritable. Became paranoid and refused all medications after the third week and had to be dropped from study

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Special Article

A BIBLIOGRAPHY OF INTERNAL MEDICINE: AMEBIC DYSENTERY

ARTHUR L. BLOOMFIELD, M.D.

SAN FRANCISCO, CALIF.

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THE subject of amebic dysentery and amebiasis is systematically covered in a wide variety of textbooks and monographs. Leonard Rogers', *Dysenteries, Their Differentiation and Treatment* (London, 1913, Henry Frowde) gives an authoritative discussion with an excellent historical review and a good selected bibliography. Other recent books of note are those by C. F. Craig (*The Etiology, Diagnosis and Treatment of Amebiasis*, Baltimore, 1944, The Williams and Wilkins Co.), by H. H. Anderson, W. L. Bostick, and H. G. Johnstone (*Amebiasis, Pathology, Diagnosis and Chemotherapy*, Springfield, 1953, Charles C Thomas) with extensive references to the recent literature, and by E. C. Faust (*Amebiasis*, Springfield, 1954, Charles C Thomas) which gives a concise outline of the subject. Books on the parasitology of amebiasis suitable for the general reader are those of C. Dobell (*The Amoebae Living in Man*, 1919, London, John Bale, Sons and Danielsson, Ltd.), of C. Dobell and F. W. O'Connor (*The Intestinal Protozoa of Man*, London, 1921, John Bale and Danielsson, Ltd.). A somewhat more comprehensive treatise is that of M. Hartmann and C. Schilling (*Die pathogenen Protozoen*, Berlin, 1917, Julius Springer).

AMEBIC DYSENTERY

Amebic granuloma—Ref. 27.
Amebic liver abscess—Refs. 1, 2, 9, 10, 11, 13, 18, 19.
Brain abscess—Ref. 17.
Chemotherapy—Refs. 24, 26.
Clinical—Refs. 1, 2, 5, 10, 11.
Cultivation of amebae—Ref. 16.
Cysts—Refs. 12, 14.
Experimental amebiasis—Refs. 8, 12, 20, 21, 25.
General—Refs. 1, 2, 10, 11.
Histology—Refs. 7, 11.
Latent amebiasis—Refs. 16, 23.
Parasitology—Refs. 4, 5, 6, 7, 8, 10, 11, 13, 16.

Supported by a grant from the California Foundation for Medical Research.

Toxicity of emetine—Ref. 22.
Treatment with emetine—Ref. 19.
Treatment with ipecac—Refs. 3, 18.

1. Annesley, James: Researches into the Causes, Nature and Treatment of the More Prevalent Diseases of India, and of Warm Climates Generally, London, 1828, Longman, Rees, Orme, Brown and Green, 2 vols.

One cannot neglect, in the bibliography of amebic dysentery, Annesley's two monumental folio volumes. This is indeed a magnum opus. The author says in his preface: "To this end he has sedulously watched disease throughout its course; and when it proved fatal, compared the symptoms while living with the appearances after death. . . ." (preface, p. xiv). This is the keynote of the book which deals less with vague speculations than with descriptions of observed facts. The elaborate section on hepatic abscess (Vol. I, p. 516) gives first a general discussion followed by case reports. "It [hepatic inflammation] frequently supervenes to the insidious inflammation of the substance of the liver, which often accompanies, if it does not actually occasion, a particular variety of dysentery. . . ." As to dysentery (Vol. 2, Ch. IV, p. 151) he says: "In the observations which we shall have to make on this very important and prevalent disease, we shall, first, consider it in its simpler or less complicated forms; we shall next treat of that variety which is characterized by attendant disorder of the liver; and afterwards offer some remarks on the chronic forms of the disease, and on the scorbutic dysentery which is occasionally met with in intertropical practice" (Vol. 1, p. 151). He gives an excellent description of acute dysentery, but whether bacterial or amebic one cannot be sure. Section II deals with "Hepatic dysentery or dysentery complicated with disease of the liver" and this is almost surely amebic. "Hepatic dysentery assumes various forms or modifications: it is sometimes acute, but much more frequently subacute and chronic" (Vol. 1, p. 197). Like other observers at the time, Annesley was confused about the relation of dysentery and liver abscess, he was uncertain which came first and which was the cause of the other. His speculations on the cause of dysentery are disappointing in contrast to his description of cases. "The influence of the moon in the production of dysentery, as well as of fevers, has been much discussed. . . . That dysentery and fever are both observed to supervene in a manner well calculated to authorize a belief in sol-lunar influence, cannot be denied by any experienced practitioner" (Vol. 2, p. 247). "On the subject also of the infectious nature of dysentery, much has been advanced. As the disease is met with in warm climates, it seldom or never proves contagious" (Vol. 2, p. 249). Treatment consisted of bleeding, purgation, and various medicines among which ipecac is mentioned without special emphasis. The volume concludes with a series of beautiful colored plates of diseased bowels. Those of the liver (Vol. I), in many cases, picture indubitable amebic abscesses.

William Twining's book (*Clinical Illustrations of the Most Important Diseases of Bengal*, Calcutta, 1832, Baptist Mission Press) published a few years later covers essentially the same ground and contains little that is new concerning dysentery.

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2. Parkes, E. A.: Remarks on the Dysentery and Hepatitis of India, London, 1846, Longman, Rees, Orme, Brown and Green.

Parkes, working in the Indian Army medical service, had plenty of opportunity to study dysentery, and this book illustrates very well the rudimentary state of knowledge of the disease at the half-way mark of the century. Nothing was known as to cause. "I shall pass over this difficult subject rapidly, as the causes of dysentery are as undetermined as its pathology," (p. 131). There are mentioned the following causes: "all acid agents, suppression of secretions rapidly accomplished, epidemic states of the atmosphere, and alterations of blood." As to the great frequency of dysentery in India, Parkes says that discounting all other possible causes "there still must remain to be accounted for an unusual proneness in the mucous membrane of the large intestines to be acted upon by exciting causes," (p. 132). "Perhaps no individual ever can have during a life-time opportunities of accurately studying all the varieties of dysentery,—its complications with remittent fever, with cholera, with gastro-enteritis, and with typhus,—its union with scurvy and purpura, with several kinds of hepatitis, with delirium tremens, with pancreatic and spleen diseases . . . —its numerous chronic states, depending on various stages of alteration, hypertrophy, ulceration, or otherwise, of the colonic and cecal solitary glands, and thickening of the intestinal coats," (p. 137). The association of dysentery with hepatic abscess is clearly recognized, but it is not known which really comes first. "The causes of primary hepatitis, meaning by that term the low insidious suppurative form, generally in an advanced stage, complicated with dysentery, are much more obscure. The first opinion which claims our attention is that which refers the disease to the action of external heat," (p. 229). Under treatment, stress is laid on depletion—bleeding—plus a great variety of medicines. Parkes does point out however that the "large doses of ipecacuanha, viz. from 30 grs. to 1 dr. are much more efficacious" than smaller doses (p. 145). Parkes' objective descriptions of clinical cases and autopsies are refreshing in the midst of otherwise arid material.

How much of the dysentery described by Parkes was bacillary and how much was amebic remains a puzzle. There had been little progress since Annesley's vast monograph in 1828 (Ref. 1).

3. Docker, E. S.: On the Treatment of Dysentery by the Administration of Large Doses of Ipecacuanha, Lancet *2:* 113, 1858.

We cannot trace in detail the introduction of ipecac into the treatment of tropical dysentery. Apparently the drug was in common use, however, in India by the beginning of the nineteenth century. Docker, working in Mauritius, seems however to deserve the credit for using ipecac in really large and effective doses. "Out of upwards of fifty cases of dysentery I lost but one (in four years the mortality ranged from ten to eighteen percent)." He points out the "ineffectiveness" of the small amounts commonly employed. "I give it in doses ranging from ten to ninety grains. . . . In all constitutions, robust as well as delicate, under all circumstances, the result is the same. In the very worst cases . . . after the whole range of remedies has been tried in vain, the disease

running its course swiftly and surely to a fatal issue, ninety grains of ipecacuanha have been given, and forthwith the character of the disease, or, I should rather say, the character of the *symptoms* has been entirely changed; for the disease itself is literally cured, put a summary stop to, driven out." Striking illustrative cases are presented.

4. Lambl, Wilhelm: Mikroscopische untersuchungen der Darmexcrete, Vierteljahrschr. f. d. prakt. Heilk. *1:* 1, 1859.

Lambl is usually mentioned as the first observer concerned with amebae in the stools. In the above paper, however, which deals in detail with the character of the stools in disease, no mention is made of amebae, nor is anything resembling them shown in the illustrations. Under the heading of intestinal parasites only larger parasites such as tapeworms are mentioned. In his second communication (I. Theil. Beobachtungen und Studien aus dem Gebiete der pathologischen Anatomie und Histologie, Prag, Friedrich Tempsky, 1860), Lambl was no more definite, as his illustration (reproduced in Stillwell, loc. cit.) shows. Whatever the bodies pictured may be, they are certainly not amebae.

5. Lösch, F.: Massenhafte Entwickelung von Amoeben im Dickdarm, Virchows Arch. f. path. Anat. *65:* 196, 1875.

The famous case of Lösch is supposed to be the first well-described instance of amebic dysentery. It concerned J. Markow, a peasant, who was taken sick in St. Petersburg in the summer of 1871 with a stubborn diarrhea which persisted for several months. The story is that of relapses and remissions until his death in the hospital after a period of nearly three years. The stools were at times largely pus, blood, and mucus, but at times they were profuse and watery. The patient became weak, pale, and edematous, and death occurred on April 12, "with the picture of severe anemia and general exhaustion." It is of interest that Professor Eichwald, because of the anemia, suggested a transfusion which was performed on February 11 by Dr. Roussel, "with the apparatus constructed by him and 9 ounces of blood drawn from the median cephalic vein of a strong healthy man were injected directly into the cephalic vein of the upper arm of the patient. Right after this transfusion a chill occurred lasting half an hour followed by a feeling of heat. The temperature rose in three hours to 40.1° but by evening fell to 38.5." The stools showed, "in large numbers, as many as 60 to 70 or more per field, some free, some enclosed in mucus, large cell-like structures which were immediately to be recognized as parasites, in fact amebae, because of their peculiar motility." While the amebae were for a long time a constant finding, from March 11 on, "despite the greatest care no more amebae were demonstrated throughout his course." A beautiful description of the parasites is given dealing with structure, size, motility, nucleus, etc. Lösch does not, however, emphasize the presence of red blood cells in the parasites: "Aside from the nucleus, the vacuoles and the granules one observes not uncommonly in the protoplasm various formed particles taken up from the outside . . . —bacteria, vibrios, chains of mycothrix, cocci, and exceptionally larger elements such as red and white blood corpuscles." Lösch suggests the name *Amoeba coli* because the colon seemed to be its principal site and because it

was unlike any hitherto described ameba. The pictures given in Plate X are excellent; again the absence of red cells in the parasites is striking. The autopsy findings were those of an advanced cicatricial colitis; the lower ileum was also involved. "The thickening and swelling of the mucous membrane of the colon depended, as microscopic examination showed, mainly upon an inflammatory infiltration of the submucosa."

Lösch after trying numerous medicaments decided to use quinine since he found that a solution of quinine, 1 to 5000, in vitro, caused the amebae to become motionless, round and granular in one minute. Lösch gave the quinine to a patient in a clyster, 20 grams to the pound of water, after which the amebae disappeared from the stools for several days but soon reappeared. This observation was the start of chemotherapy for amebiasis, although all early efforts were with solutions used locally rather than systemically.

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Lösch analyzes the case in relation to the amebae and concludes, "One must therefore assume that Markow sickened first with dysentery and that only later did the amebae enter the bowel and grew there, and there maintained the inflammation."

Is this suggestion of Lösch correct? It must be admitted that the clinical features—a sporadic case in a cool climate, the long duration with remissions and exacerbations, the character of the stools, the final disappearance of the amebae—suggest ulcerative colitis rather than amebic dysentery. However, the huge numbers of amebae are hard to explain in any other than a causal role, even though the paucity of ingested red cells within the amebae is striking.

Lösch also reports some experiments in which he fed to dogs or injected into the rectum of dogs stools from the patient. Three of four experiments were "entirely negative." The results in the fourth are hard to interpret. Globules of mucus adhering to particles of formed stool contained many amebae some days after inoculation. The animal did not seem ill and was sacrificed on the eighteenth day. There were three superficial ulcerations in the rectum. It is impossible to say whether Lösch really produced amebic dysentery; subsequent writers have usually found dogs refractory to the experimental disease.

The exact interpretation of Lösch's case is therefore not entirely clear.

6. Kartulis [S.]: Zur Aetiologie der Dysenterie in Aegypten, Virchow's Arch. f. path. Anat. *105:* 521, 1886.

Kartulis was evidently alert to the possibility of amebae in stools since he raises the question in connection with certain bodies which he found (Ueber Riesen-Amöben (?) bei chronischer Darmentzündung bei Aegypter, ibid. *99:* 145, 1885) in the stools of a boy who had suffered from dysentery several months previously. It is obvious from the description and the drawing that these bodies, queried by Kartulis himself, are not amebae at all. But a year later, Kartulis unequivocally describes amebae which were found "in every case of undoubted dysentery. In no cases [of other disease] could I find amebas." There is a splendid description of the organisms which leaves no doubt as to their nature, although Kartulis mentions slight differences between his

and Lösch's (Ref. 5) amebas. Kartulis went beyond Lösch in describing amebae in stained sections of bowel. Alcoholic solutions of methylene blue and gentian violet were especially suitable. The parasites were seen most abundantly in fresh ulcers. "In several preparations the amebas were present in such numbers that the whole submucosa seemed full of them." "Their form in sections is usually round or oval." Kartulis was unable to cultivate the amebae. He found them dead in stools in twenty-four hours; in sugar or salt water they died in a few hours. In hanging drop, they survived for twelve hours. Introduction of amebae into the colons of two guinea pigs and one rabbit was without result. The amebae were found in all stages of dysentery. "That the amebae must be accepted as the cause of tropical dysentery seems definite on the basis of what has been reported. But how the organisms enter and succeed in developing in the colon is hard to explain." Kartulis' work is impressive and he clearly established amebae as the cause of dysentery although his finding of their invariable presence in dysentery and invariable absence in other diseases is perhaps to be questioned. Later N. G. Masiutin (Ob amoebakh kak tchougeiadnykh, tolotiakh kislok, Vrach. *10:*557, 1889*) [German abstract: Ueber die Amoeben als Parasiten des Dickdarms, Centralbl. f. Bakt. *6:* 451, 1889] found amebae similar to those of Lösch in five patients suffering from various bowel disturbances including one of "typhoid" fever. For this reason he doubted the primary etiologic role of amebae, but suggested that they entered the body in drinking water, multiplied, and were a factor in keeping up a disease process caused by some other agents. Like his predecessors, he prescribed clysters of various substances. He regarded quinine as the most effective of these in extirpating the amebae and allowing the disease process to subside. Kartulis (Ueber weitere Verbreitungsgebiete der Dysenterie-Amoeben, Centralbl. f. Bakt. *7:* 54, 1890) disputed Masiutin's doubts about the causal role of amebae and reported two cases of dysentery (which he examined on a visit to Greece) in whose rectal discharges the same amebae were found which he saw in Egypt. He thought that Masiutin's observations simply widened the field of symptom complexes which could be produced by these amebae. One gets a picture of the doubts and speculations of the early observers as to the true role of these animalcules in disease.

7. Koch, Robert: Bericht über die Thätigkeit der zur Erforschung der Cholera im Jahre 1883 nach Egypten und Indien entstandten Kommission. Arb. a. d. k. Gsndhtsamte *3:* Anlage VI, p. 63, 1887.

Koch made careful autopsies as early as 1883 not only on cholera patients but on people dead of other diseases; there were five instances of dysentery of which two were complicated by liver abscess. "There were found in the bases of fresh ulcers [in the colon] in addition to innumerable bacteria peculiar amebalike structures." These bodies were only seen in sections of the ulcers or in material taken from them rather than in the stools, a fact which to Koch indicated "a close relation to disease." Amebae were also seen in the capillaries

*I am indebted to Mrs. A. Hoen for the correct transcription of this title from the original Russian.

near a liver abscess. Koch was evidently the first to recognize amebae in stained sections of tissue but he does not seem to have pursued the matter further himself, although Kartulis, his pupil, acknowledges Koch's influence (Ref. 6).

8. Hlava, Jaroslav: O úplavici Předběžné sdělení, Časopis Lékařův Ceských *26:* 70, 1887. [Abstract by Kartulis: Centralbl. f. Bakt. *1:* 537, 1887.]

We have not seen the original article which is described in the interesting paper by G. G. Stillwell (Amoebiasis: Its Early History, Gastroenterology *28:* 606, 1955). Stillwell points out the error which Kartulis made in his abstract in setting down "O. Uplavici" ("on dysentery") as the author's name. Hlava had sought for bacteria in the stools of dysentery patients but as he convinced himself that no constant bacterial form was present he looked for amebae. In 60 cases (some sporadic, others endemic) he always found amebae in the fresh stools. He injected ameba-containing stools into the rectums of 17 dogs with two positive results, of 6 cats with four positive results and of a number of rabbits, chickens, and guinea pigs with no reaction. Since dysentery was transmissible to cats the writer concluded that the ameba was the cause of dysentery. Finally he reports a case with giant amebae. With these amebae he infected a cat and again recovered giant amebae from it. These observations were carried on in Prague, not in the tropics, and one can not help feeling some reservations about them. It is, however, of interest that cats (or at least kittens) have turned out to be the most satisfactory animals for experimental amebiasis.

In setting the record straight about Dr. Hlava one should refer to C. Dobell's article (Dr. O. Uplavici (1887-1938), Parasitology *30:* 239, 1938) where this comedy of errors is fully explained.

9. Kartulis [S.]: Zur Aetiologie der Leberabscesse. Lebende Dysenterie-Amoeben im Eiter der Dysenterischen Leberabscesse, Centralbl. f. Bakt. *1:* 681, 1887.

"The constant finding of amebae in every case of dysentery impelled me to look for them in the liver abscesses which complicate this disease." Amebae were found in all of twenty cases. Kartulis reports an instance in which the abscess had ruptured into the pleura; the patient died shortly after thoracotomy. The pus at autopsy from an intact liver abscess showed the amebae "practically in pure culture." Bacterial cultures were made in four cases and various organisms were obtained. Kartulis regarded these as secondary invaders which entered with the amebae. A little later he (Ueber tropiche Leberabscesse und ihr Verhältniss zur Dysenterie, Virchow's Arch. f. path. Anat. *118:* 97, 1889) discusses critically the whole subject of tropical liver abscess in relation to dysentery. He concludes: "From what has been said it seems probable that in Egypt amebae play an etiological role in the genesis of dysenteric liver abscess, and that pyogenic bacteria, probably originating in the gastro-intestinal tract cause idiopathic liver abscess."

There is an immense literature on hepatic amebiasis which we can not review further; the reader is referred to sections on the subject in all of the books to which reference is made in the introduction. Recently, however, N. J. Conan,

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Jr. (The Treatment of Hepatic Abscess With Chloroquine, Am. J. Med. *6:* 309, 1949) recommends chloroquine as a specific; his work is confirmed by W. A. Sodeman, A. A. Dolvinen, E. M. Gordon, and C. M. Gillikin (Chloroquine in Hepatic Amebiasis, Ann. Int. Med. *35:* 331, 1951).

10. Osler, William: On the Amoeba Coli in Dysentery and in Dysenteric Liver Abscess, Bull. Johns Hopkins Hosp. *1:* 53, 1890.

Osler was the first on this side of the Atlantic to describe amebae in dysentery and liver abscess. "Dr. B., age 29, resident in Panama for nearly six years . . . had a chronic dysentery . . . he began to have an irregular fever with occasional chilly sensations and sweats, to lose flesh and to have a very sallow complexion. . . . He had six or eight mucoid stools with traces of blood daily." Liver abscess was diagnosed and evacuated surgically. Osler found in the pus "in large numbers the amoebae which Kartulis had described. . . . The material was taken at once to the Pathological Laboratory where Prof. Welch and Dr. Councilman confirmed the observation. . . . After the operation the dysenteric symptoms did not abate in the slightest; he continued to have from eight to sixteen movements daily." Osler then gives a detailed description of the amebae, drawings of which are reproduced for the first time in Stillwell's article (Ref. 8). Osler concludes: "It is impossible to speak as yet with any certainty as to the relation of these organisms to the disease. The subject is deserving of extended study, and a point of special interest will be the determination of their presence in the endemic dysentery of this country."* Shortly after this, Lafleur (Demonstration of Amoeba Coli in Dysentery, Bull. Johns Hopkins Hosp. *1:* 91, 1890) reported a case of dysentery in a sailor on a steamship sailing between Baltimore and Bremen "in which the Amoeba Coli had been found in the stools, and exhibited the living parasite under the microscope." The patient had been in the tropics in 1880. A third case was soon reported by Simon (Abscess of the Liver, Perforation Into the Lung; Amoeba Coli in Sputum, Bull. Johns Hopkins Hosp. *1:* 97, 1890). The patient had been in the West Indies in 1883 but was quite well when there. He developed diarrhea and cough and "on the day of admission the expectoration was noticed to be a peculiar rusty, reddish-brown color purulent and resembling anchovy sauce. Actively moving amoebae were found in it, a fact which at once called attention to the bowels and to the liver. . . . Our attention would never have been called to his actual condition by the character of the stools. As they looked perfectly healthy, with simply adherent mucus, we should probably have regarded the case as one of pleurisy." The atmosphere at Johns Hopkins, thus, was ripe for the work of Councilman and Lafleur (Ref. 11).

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*On March 20, Osler wrote to Musser as follows: "We have been much excited over Kartulis' amoebae which we have found in a liver abscess from a case of dysentery—a Dr. from Panama. They are most extraordinary and striking creatures and take one's breath away at first to see these big amoebae—10-20 times the size of a leucocyte—crawling about in the pus. The movements are very active and in one case kept up for 10 hours. I get a fresh stock of pus from the drainage tube every day so if you could run down some eve. we could look for the creatures in the morning. . . . Keep an eye on your Blockley dysenteries as it would be most interesting to find similar bodies in our dysenteries." Harvey Cushing, The Life of Sir William Osler, Oxford, 1926, Vol. 1, p. 326.

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From this time on there were various confirmatory reports of the presence of amebae in dysentery and liver abscess. They are carefully reviewed by Councilman and Lafleur.

11. Councilman, W. T., and Lafleur, H. A.: Amoebic Dysentery, Johns Hopkins Hosp. Reps. *2:* 395, 1891.

This monograph of some 150 pages, stimulated by the cases seen at Johns Hopkins (Ref. 10) is indeed a landmark in the study of the subject. "In this article we propose to consider a disease which is characterized by definite pathological lesions, and is separated not only by its destructive pathological anatomy, but also by its aetiology and clinical history from other affections of the intestines with which it has hitherto been classed under the general name of dysentery." Councilman and Lafleur were therefore the first to define amebic dysentery unequivocally as a specific disease, and indeed to give it a specific name and to rename its causal agent "Amoeba dysenteriae." They give a detailed description of the parasites and emphasize the presence in them of red blood cells, "as many as six or eight having been seen in a single amoeba." They describe and picture the appearance of dead amebae stained in various ways. They report fifteen cases of amebic dysentery and give a classical clinical analysis of every feature of the disease. The section on hepatic abscess is specially important and they point out the frequency of this complication in patients who have no overt dysentery. Modern study has added little to this definitive analysis. As to therapy, "Ipecacuanha was administered in case VIII after the manner recognized by surgeons in India," and, in other cases, "quinine was given by mouth, on theoretical grounds rather than from empirical evidence as to its value." Clysters of quinine as well as of bichloride of mercury, 1:5000 or 1:3000, were employed in two cases. Each clyster was retained for ten to fifteen minutes. "The results achieved are not brilliant but warrant a more extended trial. This much can be said, that quinine injections do destroy amoebae in the contents of the bowel, but whether they reach and destroy the amoebae in the tissues is an open question." The section in which the pathologic lesions are meticulously described is one of the outstanding features of this monograph. The writers thought the amebae produced a necrosis of tissue and exercised a solvent effect on the intercellular substance. "The ulceration is produced by infiltration of the submucous tissue and necrosis of the overlying mucous membranes, the ulcer in consequence having the undermined form. Frequently in addition to the ulcers there is infiltration of the submucous tissue without ulceration. In all of these lesions unless complicated by the action of bacteria there is absence of the products of purulent inflammation." "These abscesses [of the liver] differ in their anatomical features from those produced by other causes. The chief difference is found in the absence of purulent inflammation, the abscess being caused by necrosis, softening and liquefaction of the tissue. In these liver abscesses the amoebae are not associated with any other organism." "This is the form of dysentery which has been commonly called tropical dysentery." There are numerous reproductions of microscopic sections of the lesions and colored drawings of stained amebae showing their structure. There is a bibliography of 98 pertinent titles.

This monograph is a definitive account of the disease which has hardly been superseded to the present day.

12. Quincke, H., and Roos, E.: I. Ueber Amoeben-Enteritis, Berl. klin. Wchnschr. *30:* 1089, 1893.

Quincke and Roos made notable contributions to the subject. They were the first to describe cysts. "Of special importance is the encysted condition of the amebae. These forms are considerably smaller, have a diameter of 10-12 μ, a much sharper if not definitely doubled contour; they appear shiny, transparent, and show the nucleus very unclearly." "Very noteworthy is the great 'haltbarkeit' of these encysted forms; in the moist chamber as well as in the stools they could still be recognized after 20 days but not after 4 to 8 weeks." Whereas the vegetative forms injected into the rectum of kittens caused dysentery, they were harmless when given by mouth; on the other hand the cysts produced disease when fed. Another important finding was the discovery of other amebae in the bowel definitely different from those associated with severe dysentery. "There are similar but milder forms of endemic dysentery; the parasite causing them (Amoeba coli mitis) is different from the Amoeba coli of Lösch and is not pathogenic for kittens. One ameba often found in healthy people and doubtless harmless (A. intestinalis vulgaris) is probably different from both." A little later Roos (Zur Kentniss der Amoebenenteritis, Arch. f. exper. Path. u. Pharmakol. *33:* 389, 1894) pursued the subject further. He reports elaborate observations on production of dysentery in cats by rectal instillation of material containing amebae and by introducing cysts into the stomach. On the other hand no disease was produced by stools containing *Amoebae coli mitis.* "According to our experiments infection with the parasites probably results from the ingestion of cysts of amebae by mouth." This work was later confirmed by R. P. Strong and W. E. Musgrave (Preliminary Note Regarding the Etiology of the Dysenteries in Manila, Rep. of the Surg. Gen. of the Army, Washington, 1900, p. 251). Quincke and Roos therefore opened the way to the discovery of the mode of transmission of amebic dysentery.

Meanwhile there appeared a comprehensive review by A. Schulberg (Die parasitischen Amöben des menschlichen Darmes, Centralbl. f. Bakt. *13:* 598, 654, 701; 1893) with a subtitle of "Critical Review of the Development of Current Knowledge." Schulberg analyzes the conflicting claims in the literature with regard to the pathogenicity of amebae found in the bowel, with bibliography of some 50 titles.

13. Kruse, W., and Pasquale, A.: Untersuchungen über Dysenterie und Leberabscess, Ztschr. f. Hyg. *16:* 1, 1894.

In this tremendous communication of 149 pages on amebic dysentery and liver abscess, Kruse and Pasquale reported confirmation of much of the earlier work, as well as many experiments in which the disease was successfully transmitted to kittens. They used pus from liver abscesses and produced dysentery in three experiments. "In two of these three experiments pus was used which the microscope and culture showed was completely sterile apart from the amebae." Thus they made the important observation that amebae alone could produce

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dysentery without the associated activity of bacteria as many had insisted. Indeed at that time the view was prevalent that amebae were "opportunists" which took advantage of existing lesions to invade and aggravate them. Thus, as keen an observer as George Dock (Observations on the Amoeba Coli in Dysentery and Abscess of the Liver, Daniels' Texas M. J. *6:* 419, 1891), after finding amebae in a variety of apparently poorly related conditions, concludes, "We have no reason for ascribing pathogenic powers to the parasite, though the evidence is such that it offers a promising field for future investigations."

14. Huber: [Demonstration of Dysentery Amebae.] Deutsche med. Wchnschr. *29:* 267 (No. 34), 1903.

"Further I would like to call attention to one important finding . . . namely small, delicate, spherical cysts which I must conclude are encysted forms of the amebae. Every time when the patient's stool became hard and the amebae disappeared, these cysts appeared, and when a relapse occurred and amebae were again present in the stools, the cysts disappeared. . . . Furthermore, I have been able to infect animals per os with such cyst-containing stools. The cysts found by me are distinguished from those of the ordinary ameba which Schaudinn has exactly described. Unstained the nucleus is very hard to recognize. In stained preparations the nucleus is more prominent as a delicate chromatinpoor ring. . . . On occasion one finds two or four nuclei."

With this classic description Huber amplified that of Quincke and Roos (Ref. 12). He pursued the subject further in a more comprehensive article (Untersuchungen über Amöbendysenterie, Ztschr. f. klin. Med. *67:* 262, 1909).

15. Schaudinn, Fritz: Untersuchungen über die Fortpflantzung einiger Rhizopoden (Vorläufige Mittheilung), Arb. a. d. k. Gsndhtsamte *19:* 547, 1903.

Fritz Schaudinn, the great discoverer of the spirochete of syphilis, erred as badly in his interpretation of the life cycle of amebae as he had in his studies of invasion of red cells by sporozoites in malaria. Part of his work, on the vegetative forms of amebae, was sound and he coined the name "Amoeba histolytica." "I choose to call them *Entamoeba histolytica* because of their capacity to destroy tissue." But he went wrong in his interpretation of encystment and his belief that he had demonstrated multiplication by sporulation. Schaudinn's authority confused the subject for many years; the details of the story are given in Stillwell's article (Ref. 8).

16. Musgrave, W. E., and Clegg, Moses T.: Amebas: Their Cultivation and Etiological Significance, Bureau of Government Laboratories, Manila, Oct. 1904, No. 18.

Musgrave and Clegg first reviewed the conflicting literature on attempts to grow amebae outside the body. They succeeded with various strains on a medium whose base was agar, sodium chloride, and extract of beef, provided the amebae were grown in symbiosis with pure cultures of bacteria which favored their development. "Amebas are the etiologic factors in the disease generally known as amebic dysentery, and by following the methods described in this paper, such amebas may be grown on artificial media, and the disease reproduced in monkeys and man by the ingestion of these cultures. Amebas may be re-

claimed by culture from the stools or the intestinal ulcers." They conclude that "All amebas are or may become pathogenic. This proposition, pending a complete solution of the problem, is the only safe one to adopt from the standpoint of public health in the Tropics." Musgrave and Clegg also introduced the term "amebiasis." "The term amebiasis, which has been introduced in this article, denoting an infection with amebas, is comparable in its application to filariasis, trypanosomiasis, uncinariasis, etc. It is not open to the objections so frequently offered to 'amebic dysentery,' 'amebic enteritis,' and the other names usually given to the disease." Musgrave (Intestinal Amoebiasis Without Diarrhoea, Philippine J. Sc., B. Medical Sciences: 229, 1910) later reported patients who died of various conditions, mostly unrelated to amebic infection, and usually without bowel symptoms, but who at autopsy showed "characteristic amoebic lesions." Such symptoms as abdominal "aching," flatulence, constipation, distention, and loss of weight were noted in some patients. "When we come to study the clinical phenomena shown by this class of cases, it is seen that there is nothing specific or definite in any one, or in all the findings, except the one of the presence of amoebae in the stools."

E. L. Walker (A Comparative Study of the Amoebae in the Manila Water Supply, in the Intestinal Tract of Healthy People, and in Amoebic Dysentery, Philippine J. Sc., B. Medical Sciences *6:* 259, 1911) had been working on the problem of amebas for some years. "It has been my experience . . . that if the character of both the trophozoite and the cyst be taken into consideration, they can always be separated into species having well defined morphological characteristics." He was able to confirm Musgrave and Clegg in so far as it was possible to cultivate amebas by their methods, but only nonpathogenic amebas derived from the Manila water supply. "The amoeboid organisms parasitic in the intestinal tract of man belong to a distinct genus, *Entamoeba*. . . . The entamoebae are strict or obligatory parasites and are incapable of multiplication outside the body of the host. They can not be cultivated on Musgrave and Clegg's medium." Walker emphasized the morphologic differences between *Entamoeba histolytica* and the harmless *Entamoeba coli*. "The infection with *Entamoeba histolytica* may persist for an indefinite period after the symptoms of amoebic dysentery have disappeared, during which time the resistant encysted entamoebae may be passed in large numbers in the stools and constitute an important source of infection to others. Such persons are 'carriers' of amoebic dysentery, comparable to the 'carriers' of typhoid fever or cholera. The prophylactic measures for the prevention of amoebic dysentery are sufficiently indicated by the preceding conclusions; they are identical with those required for prevention of other specific infectious diseases of the intestinal tract, like typhoid fever and cholera." There are reproductions of excellent drawings of the various types of amebae. The importance of Walker's observations cannot be overestimated.

While the work of Musgrave and Clegg was not generally accepted, D. W. Cutler (A Method for the Cultivation of *Entamoeba histolytica*, J. Path. and Bact. *22:* 22, 1918) described a method "by which E. histolytica can be maintained in culture for several months. These cultures, if inoculated into cats, produce

dysenteric lesions of the intestines." He found that cysts could be produced in cultures by omitting to sub-culture for four or five days. W. C. Boeck and J. Drbohlav (The Cultivation of Endamoeba Histolytica, Am. J. Hyg. *5:* 371, 1925) later also claimed to have cultivated pathogenic amebae and to have produced lesions in kittens with culture material. They were unable, however, with their method, to produce encystment. The work of Cutler has been sharply criticized by C. C. Dobell (loc. cit., The Amoebae Living in Man, p. 70). A summary of the whole problem of cultivation of amebae is to be found in Anderson, Bostick and Johnstone (loc. cit., p. 346, et seq.).

17. Kartulis [S.]: Gehirnabscesse nach dysenterischen Leberabscessen, Centralbl. f. Bakt. *37:* 527, 1904.

Kartulis reviews the meager literature on brain abscess occurring in association with dysentery, and reports two cases of his own in which he found amebae both in the pus and in sections of the wall. The subject is reviewed in detail by J. A. Orbison, N. Reeves, C. L. Leedham, and J. M. Blumberg (Amebic Brain Abscess: Review of the Literature and Report of Five Additional Cases, Medicine *30:* 247, 1951). This article has a bibliography of 82 titles.

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18. Rogers, Leonard: The Prevention and Treatment of Amoebic Abscess of the Liver, Philippine J. Sc. B. Medical Sciences: 219, 1910.

Rogers was the first to insist on the value of ipecac in the treatment of amebic hepatitis and abscess of the liver. He points out that 86 per cent of a large series of liver abscesses were sterile as far as bacteria were concerned, although in a few cases "numerous cocci and bacteria are found." "Lastly, I would urge that every patient operated on for amoebic-liver abscess should be given a course of full doses of ipecacuanha as soon as possible, with the view to healing the ulcers in the large bowel, which have originated the hepatic trouble and are often latent and give rise to no symptoms."

19. Rogers, Leonard: The Rapid Cure of Amoebic Dysentery and Hepatitis by Hypodermic Injections of Soluble Salts of Emetine, Brit. M. J. *1:* 1424, 1912.

Rogers briefly tells the story of ipecac in the history of medicine. "The Brazilian root was first brought to Europe by Piso in 1658, and was successfully used by Helvetius in the treatment of Louis XIV, and sold as a secret remedy to the French Government." Turning however to emetine, Magendie and Pelletier (Sur l'Émétine et sur les trois espèces d'ipecacuanha, J. Gén. de Méd. *59: 223,* 1817) extracted an alkaloid from various types of ipecac; the ligneous internal part of brown ipecac, psycotria emetica, contained for example 1.15 parts of "emetine." This material taken by mouth in one or two gram doses produced vomiting just as did ipecac. Six to 12 grams killed a dog. Finally the authors advised giving emetine in a sort of camomile tea in which "it is agreeable even to infants." The Academy approved the report and thought "emetine" worthy of further clinical study; although no results were reported in tropical dysentery. H. B. Paul and A. J. Cownley (The Chemistry of Ipecacuanha, Pharm. J. and Trans. *53* (3 Ser., Vol. 24); 61, 1893) showed that

the "emetine" of earlier workers was really a mixture of several alkaloids. It was not until many years later that E. B. Vedder (A Preliminary Account of Some Experiments Undertaken to Test the Efficacy of the Ipecac Treatment of Dysentery, Bull. Manila Med. Soc. *3:* 48, 1911), using cultures of nonpathogenic amebae, showed that both ipecac and emetine killed the organisms in the test tube. Some preparations of emetine were effective in dilutions of 1:200,000. Vedder concludes: "I would state my belief that the ipecac treatment of dysentery caused by protozoa should not on light grounds be set aside in favor of any other, but that in using this treatment great care should be taken to make sure that the dysentery is truly caused by protozoa and is not bacillary, and also to obtain an ipecac that is shown by critical analysis to contain its proper amount of emetin, and when this is not possible, to insist upon obtaining the Brazil root." It is to Rogers, however, that credit clearly goes for introducing the use of hypodermic injections of emetine in the treatment of amebiasis. Three brilliantly successful cases are reported. Rogers (Further Experience of the Specific Curative Action in Amoebic Disease of Hypodermic Injections of Soluble Salts of Emetine, Brit. M. J. *2:* 405, 1912) soon reported 12 further cases of various types of amebic dysentery and liver abscess cured by emetine. "We have, then, in my method of the subcutaneous injection of soluble salts of emetine a specific treatment of amoebic hepatitis and amoebic dysentery, which is so rapidly beneficial in the latter as to be also of great diagnostic value between that and other causes of the passage of blood and mucus in the stools. Yet, strange to say, this remarkable remedy—probably the most specific in the whole range of medicine, not excluding quinine and salvarsan—has for long been thrown away by those who pinned their faith on ipecacuanha sine emetina."

This paper really opened the modern era of chemotherapy of amebiasis; like similar efforts in other fields it was destined to be to some extent a disappointment since it was soon discovered that emetine was often inadequate to extirpate fully the infection so that relapses were prone to occur. Rogers also devotes a chapter in his book (loc. cit., p. 117) to ipecac and emetine in amebic dysentery.

Emetine was soon combined with iodine and bismuth (E.B.I., emetine bismuthous iodide) and was first tried on man in 1916 by G. C. Low and C. Dobell (Three Cases of Entamoeba Histolytica Infection Treated With Emetine Bismuth Iodide, Lancet *12:* 319, 1916); G. C. Low (Emetine Bismuth Iodide in Amoebic Dysentery, Amoebic Hepatitis, and General Amoebiasis, Lancet *1:* 482, 1917). It seemed more effective than emetine in eradicating cysts and in treating the chronic tissue stages of the disease, and is still widely used in England.

20. Walker, E. L., and Sellards, A. W.: Experimental Amoebic Dysentery, Philippine J. Sc., B. Tropical Medicine *8:* 253, 1913.

Walker and Sellards set about to prove that amebae really were the cause of "amebic" dysentery, by reproducing the disease experimentally. The results of these elaborate investigations are quite clear. First Walker re-emphasizes the necessity in practice of distinguishing the harmless *E. coli* from the pathogenic *E. histolytica* in the stools of patients. The differential features of both

the motile stage and the encysted stage are clearly listed in tabular form. Volunteers were then fed cysts of the various strains. Those who ingested *E. coli* developed no disease whereas dysentery was produced in some of those who received "histolytica" cysts. Furthermore, many of those who did not develop clinical dysentery became "carriers." Walker and Sellards drew the important final conclusion that *Entamoeba histolytica* was to all intents the sole cause of amoebic dysentery and therefore exact diagnosis was of the utmost importance. They also emphasized that vegetative forms did not survive outside the body but that cysts were the important element in transmission of the disease. Consequently the recognition of "carriers" of cysts was the key to intelligent public health preventive measures.

As to treatment, the important statement is made: "The evidence . . . points to the conclusion that the ordinary routine treatment with ipecac, while efficient in relieving attacks of dysentery and in causing the entamoeba to disappear temporarily from the stools, frequently does not kill all of the entamoebae in the intestine; consequently the patient is liable to a relapse of the dysentery."

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21. Sellards, A. W., and Baetjer, W. A.: The Propagation of Amoebic Dysentery in Animals and the Recognition and Reproduction in Animals of Atypical Forms of the Disease, Am. J. Trop. Med. *2:* 231, 1914.

Sellards and Baetjer summarize their work on experimental amebic dysentery. Employing the device of injecting the stools containing amebae from acute attacks of dysentery directly into the cecum of kittens, they succeeded in producing amebic infection in nearly 100 per cent of the animals, and in propagating the disease through eleven generations. They produced acute fatal infections, chronic infections with relapses and liver abscess, and carriers. They succeeded in increasing the virulence of the infection on repeated passages in contrast to the usual reports of attenuation. Their work was of great importance in so far as Sellards and Baetjer developed a valuable experimental tool. H. H. Dale and C. Dobell (Experiments on the Therapeutics of Amoebic Dysentery, J. Pharmacol. & Exper. Therap. *10:* 399, 1917) produced amebic dysentery in kittens by injecting material high into the colon through a glass nozzle. They studied the effect of emetine on the experimental disease. "Experimental dysentery in kittens was refractory to all kinds of treatment. Neither the ipecacuanha alkaloids, nor other substances having a powerful action on the amoebae in vitro, could cure the infection or definitely modify its course." They therefore concluded that the theory of direct amebicidal action of emetine on the parasite was no longer tenable.

In this connection one should not fail to mention the early systematic experiments on production of amebic dysentery in cats and kittens by F. Kovács (Beobachtungen und versuche über die sogenante Amoebendysenterie, Ztschr. f. Heilk. *13:* 509, 1892). His paper opens with one of the best reviews we have found of early work on relation of amebas to dysentery.

22. Levy, R. L., and Rowntree, L. G.: On the Toxicity of Various Commercial Preparations of Emetine Hydrochloride, Arch. Int. Med. *17:* 420, 1916.

In this important study, the writers review the earlier literature, and report several new cases of emetine poisoning. Bowel and cardiac disturbances are

described. In animals they were able to produce ventricular fibrillation, confirmed by the electrocardiograph. They point out that toxic effects are largely the result of overdosage and that intravenous injection is usually unnecessary. "One third of a grain three times a day for a week or ten days is usually a safe dosage." S. Dack and R. E. Molostok (Cardiac Manifestations of Toxic Action of Emetine Hydrochloride in Amebic Dysentery, Arch. Int. Med. *79:* 228, 1947) have recently reviewed the subject as have G. Klatstein and H. Friedman (Emetine Toxicity in Man, Ann. Int. Med. *28:* 892, 1948). The latter paper contains a comprehensive bibliography.

Earlier papers of interest on ipecac poisoning are those of D. Duckworth (Observations Upon the Action of Ipecacuanha and Its Alkaloid Emetia, St. Barts. Hosp. Reps. *5:* 218, 1869) who reviews previous experiments and reports observations on the gross effects of the drug in animals, and of v. Podwyssotzki (Beiträge zur Kentniss des Emetins, Arch. f. exper. Path. u. Pharmakol. *11:* 231, 1879) who made a systematic study of the drug using classical pharmacologic technique. His description of the action on the exposed frog heart with progressive irregularity until "finally the entire heart remains in an exquisite paralytic diastolic standstill" is very vivid.

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23. Thomson, J. G.: Human Entamoebiasis in Temperate Zones, J. State Med. *33:* 563, 1925.

Musgrave (Ref. 16) had already introduced the idea of "amoebiasis" and of "carriers." The concept rapidly gained acceptance and it was soon found that amebae could be found frequently in apparently healthy people outside of the "tropics." Thomson gives an elaborate table of reports on the incidence of amebas in persons some of whom were never out of the temperate zone. "It can be said . . . that an amoebic infection is, in the majority of instances, an insidious disease of such a mild character as to pass unnoticed by the patient, and while it may be true that a "contact carrier" may remain apparently healthy all his life, there is no method of accurately telling what pathological lesions are produced except in the post-mortem room." W. M. James (Diagnosis of Intestinal Amebiasis, J.A.M.A. *89:* 1469, 1927) points out the difficulty of accurate diagnosis of intestinal infection with histolytica and also gives figures on incidence. C. A. Kofoid (Statistical Summary of Persons Examined for Protozoa and Worms, etc., Twenty-Ninth Biannual Report of the State Board of Health of California, Sacramento, 1926, p. 93) gives the widely quoted figure of 13.1 per cent incidence of *Endamoeba dysenteriae* among some 1600 "healthy" people. J. F. Kessell and V. R. Mason (Protozoan Infection of the Human Bowel, J.A.M.A. *94:* 1, 1930) arrived at a similar figure in the Los Angeles County Hospital. An especially valuable review of this whole subject is that of W. C. Boeck (Survey of 8,029 Persons in the United States, for Intestinal Parasites, With Especial Reference to Amoebic Dysentery Among Returned Soldiers, Hygienic Lab. Bull. No. 133, Washington, 1923, p. 1). At any rate it is clear that there exists a widespread incidence of bowel infestation with these parasites, a far cry from the original view that there existed only vegetative forms associated with acute dysentery.

24. Reed, A. C., Anderson, H. H., David, N. A., and Leake, C. D.: Carbarsone in the Treatment of Amebiasis, J.A.M.A. *98:* 189, 1932.

For a decade after its introduction by Rogers (Ref. 19), emetine had no serious contenders in the field of therapy of amebiasis, although it was soon realized that relapses were common and that complete cure was effected in only 28 to 70 per cent of the cases (Ref. 20). Serious toxic effects also turned out to be not uncommon (Ref. 22). Attention was therefore soon turned to other drugs which might be useful; and in subsequent years innumerable preparations have been tried which cannot all be reviewed here. For the earlier literature the reader is referred to the review by O. Willner (Remedies Recently Introduced in the Therapy of Amoebiasis, Medicine *6:* 341, 1927) and to the excellent paper by C. D. Leake (Chemotherapy of Amebiasis, J.A.M.A. *98:* 195, 1932). Later reviews are those of G. A. Martin and associates: (Comparative Efficacy of Amebicides and Antibiotics in Acute Amebic Dysentery, J.A.M.A. *151:* 1055, 1953) and of H. E. Hamilton (Treatment of Amoebiasis, Arch. Int. Med. *94:* 612, 1954).

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Carbarsone (4-carbamino-phenyl arsonic acid) is one of the few earlier drugs which has stood the test of time. Reed and his associates report a careful clinical study with good results. "More closely than any other drug now exploited does carbarsone meet the requirements of an ideal antiamebic agent. It is clinically nontoxic in effective doses; it may conveniently be administered orally without interference with the patient's usual routine; it has no untoward side actions and it is comparatively cheap."

Hamilton's review (v. supr.) is especially helpful in bringing out the confused state of the subject at present. He points out that, with single drugs, relapse rates have been disappointingly high and that the tendency now is to use two or three agents in combination or succession. He also notes that the drugs effective in clearing the bowel infection (bowel phase) must be distinguished from those more effective against the parasites deep in the tissues (tissue phase). The drugs primarily effective against the tissue phase are chloroquine, emetine, and quinacrine. Of these, chloroquine (see N. J. Conan: Chloraquine in Amebiasis, Am. J. Trop. Med. *28:* 107, 1948) seems at present most safe and efficient. Hamilton also lists the drugs effective against the bowel phase, of which diiodo-hydroxyquinoline is quite satisfactory. The point of all this, however, is clear. There is as yet no entirely satisfactory drug, nor is there agreement among various observers as to which is the best. The subject is still in a state of flux.

25. Schwartzwelder, J. C.: Experimental Studies on *Endamoeba histolytica* in the Dog, Am. J. Hyg. *29:* 89, 1939.

Much work has been done in the attempt to define the mode of infection by the parasite. Schwartzwelder reviews the literature and reports his own observations on excystation in dogs, which occurred both in the ileum and in the large intestine. "The time required to bring about the process varied from 1.5 to 4.5 hours following oral inoculation with cysts." The details of invasion of the bowel by the excysted amebae are reviewed and discussed by W. M.

James (Human Amoebiasis Due to Infection With *Entamoeba histolytica*, Ann. Trop. Med. *22:* 201, 1928).

26. McHardy, G., and Frye, W. W.: Antibiotics in Management of Amebiasis, J.A.M.A. *154:* 646, 1954.

Upon the advent of the antibiotics, it was inevitable that they should be tried in amebiasis, and there are numerous papers reporting trials with one or another agent. This work is reviewed by McHardy and Frye who concluded that oxytetracycline (Terramycin) is the broad spectum antibiotic of choice, since only 8.5 per cent of relapses have been reported in the literature among 435 treated cases. "Hepatitis, hepatic abscess, and other extracolonic amebic involvements are not benefitted by treatment with the antibiotics evaluated."

27. Spicknall, C. G., and Pierce, E. C., II.: Amoebic Granuloma, New England J. Med. *250:* 1055, 1954.

The first description of "amebic tumors" is usually attributed to Kartulis (Dysenterie, Wien, 1896, Alfred Hölder, p. 60) but an inspection of his article does not make it clear that he saw localized tumors which could be, for example, confused with cancer. H. Gunn and N. J. Howard (Amebic Granuloma of the Large Bowel, J.A.M.A. *97:* 166, 1931) review the early references and introduce the term "amebic granuloma" which is now widely accepted. "The pathologic process consists in persistence of an isolated chronic ulcer with progressive erosion of the wall of the bowel. In response to the amebic ulceration and secondary infection, large amounts of edematous fibrous granulation tissue appear. . . . These granulomas may be easily mistaken for carcinoma, for they give symptoms, physical signs and radiologic appearances that may be identical with those produced by carcinoma." Spicknall and Pierce give a definitive review of the subject with a bibliography of 125 titles. The main point is the frequency of a lesion in the cecal region and the likelihood of its being confused with acute appendicitis, abscess, or tumor.

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Review

CHRONIC RELAPSING PANCREATITIS

WILLIAM W. SHINGLETON, M.D.

DURHAM, N. C.

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CHRONIC pancreatitis is a relatively common disorder of the pancreas characterized by varying degrees of abdominal pain, defective digestion, and sometimes disturbance in carbodydrate metabolism. The etiology of the disease is variable and incompletely understood; its diagnosis is often difficult, and methods of management are variable and not satisfactory in all cases. The term "chronic relapsing pancreatitis" as used in this report refers to cases in which more than one attack of acute pancreatitis, diagnosed by conventional methods has occurred, and in which the pathologic process is one of repeated acute or subacute attacks of inflammation in the gland, leading to variable degrees of destruction and fibrosis. Careful consideration of all factors bearing on the disease should be applied in every patient with the disease in order to select the method of management most likely to give the best result in each particular instance. Important in this regard is a basic understanding of the embryology, anatomy, and physiology of the pancreas.

EMBRYOLOGY AND ANATOMY OF THE PANCREAS

The pancreas, of entodermal origin, arises from two distinct primordia.[70] The dorsal pancreas arises from the duodenum, the ventral pancreas from the common bile duct. The duct of the dorsal pancreas becomes the accessory pancreatic duct (Santorini) and the duct of the ventral pancreas the main pancreatic duct (Wirsung). The dorsal pancreas and the ventral pancreas become fused, so that there is usually a communication between the two ducts. Abnormalities in embryologic development may result in the absence of the main duct, failure of the two ducts to fuse, or an abnormal attachment of the ventral pancreas,[74] causing constriction of the duodenum (annular pancreas). The primordia are originally simple tubes of entoderm and branch extensively, and by the time the dorsal pancreas and ventral pancreas fuse each has an intricate duct system. From these small ducts, tubular secretory acini are formed. During the third month of fetal life small aggregates of cells (islands of Langerhans) appear.[70]

From the Department of Surgery, Duke University School of Medicine, Durham, N. C.

The word pancreas is derived from the Greek words "pan" meaning "all" and "kreas" meaning "flesh."[70] The organ lies molded across the spinal column at the level of the first lumbar vertebra, and consists of a head, body, and tail. It is entirely a retroperitoneal organ, and lies in close proximity to the stomach, spleen, duodenum, and adrenal glands. The anatomic relations of the pancreas are shown in Fig. 1. From the standpoint of disease, the important anatomic features of the pancreas are its deeply situated retroperitoneal position, its proximity to the major blood vessels of the abdominal viscera, and its proximity to major abdominal digestive structures, especially the biliary tract and duodenum. The histologic features of the gland are: (1) acinar cells, pyramidal in shape, which form acini tubular in shape; (2) a duct system, lined by a single layer of columnar epithelium, and containing collagen with a few elastic fibers in the wall; (3) the islands of Langerhans, consisting of alpha and beta cells; and (4) interlobular connective tissues.[70]

The importance of the anatomic variations of the duct system will be discussed under etiology of pancreatitis, and innervation of the organ under physiology.

PHYSIOLOGY OF THE PANCREAS

A variety of substances elaborated by the pancreas has been identified and studied.[5,11,20,29,34,36,43] They may be divided into those elaborated by the acinar cells (the *external* secretion), and those arising from the islet cells (the *internal* secretion). A lipotrophic factor elaborated as an internal[20] and external secretion[43] has been obtained from the pancreas of the dog. In inflammatory disease of the pancreas, both external and internal secretion may be altered. In general, the external secretion is involved with digestion of foodstuffs and the internal secretion with carbohydrate metabolism. Space will not permit a detailed discussion of the relationship of the internal pancreatic secretion and carbohydrate metabolism. Two important fractions of the internal secretion are insulin and glucagon, the former supposedly secreted by the beta[12] and the latter by the alpha cells[35,76] of the islands of Langerhans. More information is needed concerning the relationship of these two substances, especially their relation to diabetes. The relationship of diabetes to anatomic changes in the islands of Langerhans is of interest. It has been reported that only 50 per cent of diabetic patients have an anatomic deficiency of islet cells.[77] Further, the diabetes which occurs after total removal of the pancreas is apt to be mild, requiring small doses of insulin, and is resistant to the development of ketosis.[25] It is apparent that the pancreas can sustain much damage without the advent of diabetes since its reserve function regarding insulin secretion is so great.

The important components of the external pancreatic secretion are *water*, *electrolytes*, and *digestive enzymes*.[70] The important electrolytes are bicarbonate, sodium, chloride, and potassium. Water constitutes 98 per cent of the secretion. The reaction is always alkaline, varying between pH 7.1 and pH 8.65. The pH is dependent on the relative proportion in the juice of the two negative ions, chloride and bicarbonate, the sum of which balances the positive sodium ions. When the bicarbonate ions increase in proportion to the chloride ions, the pH rises and vice versa.

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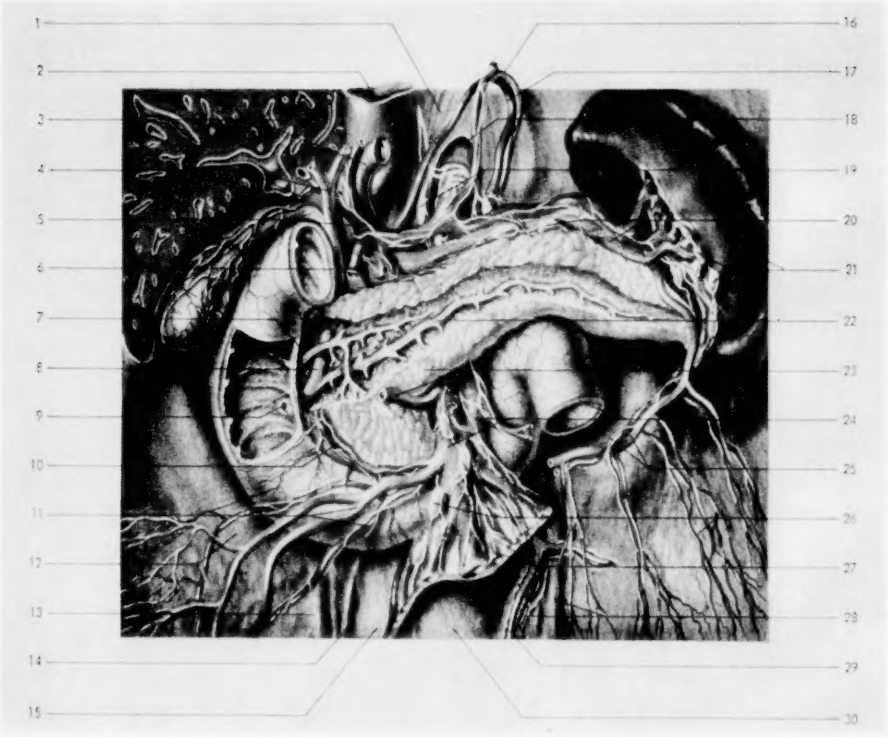

Fig. 1.—The anatomic relationship of the duodenum, pancreas, and Gallbladder (Peck). (Reproduced by permission of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.)

1. Crus of diaphragm
2. Inferior vena cava
3. Liver and portal vein
4. Hepatic duct and cystic artery and vein
5. Cystic duct and hepatic artery
6. Gastroduodenal artery and gallbladder
7. Lesser pancreatic duct
8. Common bile duct
9. Duodenal papilla (papilla of Vater)
10. Superior pancreaticoduodenal artery and vein
11. Duodenum and right colic artery and vein
12. Right kidney (in retroperitoneum)
13. Right ureter
14. Spermatic artery and vein
15. Vena cava (in retroperitoneum)
16. Left gastric artery
17. Coronary vein
18. Abdominal aorta
19. Celiac artery and right ganglion of celiac plexus
20. Superior pancreatic lymph node and splenic artery and vein
21. Spleen and splenic lymph nodes
22. Greater pancreatic duct
23. Pancreas and gastroduodenal vein
24. Jejunum and superior mesenteric artery and vein
25. Left gastroepiploic artery and vein
26. Superior mesenteric lymph nodes and omental vessels
27. Intestinal arteries and veins
28. Left ureter and left colic artery
29. Inferior mesenteric vein
30. Aorta (in retroperitoneum)

The total daily volume of external secretion has been estimated to be 700 to 800 c.c., with a slow basal secretion with fluctuations in volume of output depending upon certain controlling factors.[70]

The external secretion of the pancreas is under both nervous and hormonal control. Animal experiments performed at the beginning of the present century[49] established that the vagus nerves exert an important control over external pancreatic secretion, vagal excitation causing an increased output of juice rich in enzymes, and vagal inhibition producing the opposite effect. Thus, drugs which excite the vagus will stimulate pancreatic secretion, and those which depress vagal activity will diminish it.[4] The sympathetic nerves to the pancreas apparently do not exert an important influence over pancreatic secretion.[70]

Bayliss and Starling in 1901 discovered a substance elaborated by the duodenum and upper small intestine, later called secretin, which has a specific stimulating effect on the output of pancreatic juice. This substance, one of the first hormones to be identified, causes a larger volume of output of juice than can be obtained by vagal stimulation. This juice, however, is less rich in enzymes and contains a larger fraction of water and bicarbonate.

In addition to parasympatholytic drugs, which inhibit pancreatic secretion, it has been shown recently that chemical inhibition of carbonic anhydrase will give a similar effect.[13,78]

In the digestive process, when food enters the stomach, there occurs a reflex vagal stimulation of pancreatic secretion, and when acid chyme enters the duodenum, secretin is elaborated and causes further pancreatic stimulation.[4] Another enzyme has been described by Harper and Raper,[29] called pancreozymin, which supposedly further excites pancreatic secretion, yielding a juice rich in enzymes and similar to that obtained by vagal stimulation.

The three principal classes of digestive enzymes in the pancreatic juice are: (1) proteolytic, (2) amylolytic and (3) lipolytic. The most important proteolytic enzyme is trypsin, which is secreted by the pancreas as trypsinogen and is activated by enterokinase in the intestinal lumen. It is the most powerful proteolytic substance in the intestinal tract.[70] Amylase, the starch-splitting enzyme of the pancreatic juice, is produced in other anatomic sites in the body, e.g., the parotid, and can be measured in the blood and urine, where it rises to high levels during acute inflammation of the pancreas. Pancreatic lipase, like the other pancreatic ferments, works best at an alkaline pH. It is a powerful fat-splitting enzyme, changing neutral fat to fatty acids and glycerol, and in addition aids in the emulsification and absorption of fat. Small amounts of lipase, like amylase, can be detected chemically in the blood and urine, and high levels may occur with acute inflammations of the pancreas.[70]

ETIOLOGY OF PANCREATITIS

Experimental studies on the etiology of pancreatitis have been numerous. In 1889 Fitz[27] first described the clinical picture and related it to the pathologic anatomy of the disease. In the succeeding twelve-year period a great deal of experimental work in animals on the etiology of pancreatitis was carried out.[70]

These experimental methods for production of pancreatitis included trauma to the gland, ligation of its blood supply, ligation of the ducts, and injection of bacteria or irritating chemicals into the ducts. A wide variety of pathologic lesions was so produced, and it was generally believed that following damage to the gland there was extravasation and activation of enyzmes in the parenchymal tissue leading to autodigestion. About the same time the clinical observation was made of the frequent association of biliary tract disease and pancreatitis.

The literature on the etiology of pancreatitis indicates that from both experimental and clinical standpoints the factors involved in pancreatitis are varied. In a recent review, Ivy[32] listed 34 possible etiological factors, and even this list is not complete, since factors such as diet and anomalies of the pancreatic duct system were not included. No attempt will be made to cite evidence for and against all etiological factors that have been proposed. It is difficult to separate factors causing acute hemorrhagic pancreatitis from those causing the chronic relapsing form, since the latter probably represents repeated acute attacks. Etiological factors supposedly *initiating* pancreatitis might be placed under the following categories:

1. Obstruction to free flow of pancreatic juice
2. Stimulation of pancreatic secretion
3. Toxic agents affecting parenchyma of gland
4. Trauma
5. Vascular factors

Factors in categories one and two most often act jointly and, in my opinion, together account for the majority of cases. Categories three and five may be more important as secondary factors.

Obstruction to Free Flow of Pancreatic Juice.—There is a wide range of possible obstructive factors in pancreatitis. Congenital anomalies of the duct system of the pancreas may cause obstruction. Recently a case was described by Hughes,[30] wherein the bile duct passed anterior to the pancreatic duct, causing obstruction of the latter. Impacted stones in the lower bile duct or pancreatic duct may be the obstructing agent in some cases. Hyperplasia of the epithelium of the pancreatic duct was described by Rich[58] as an obstructing factor in some patients. Edema, and especially spasm, of the sphincter of Oddi are held by some[3,18] to be the most common variety of pancreatic duct obstruction. Tumors in and around the ampullary region may be the cause of obstruction in occasional cases. There also are certain drugs, such as codeine and morphine, which will produce muscular spasm and temporary obstruction at the ampulla.[64]

Stimulation of Pancreatic Secretion.—The stimulation of pancreatic secretion as an etiological factor in pancreatitis appears to be of importance only when concomitant partial obstruction to the free flow of pancreatic juice exists. This is certainly true of one type of experimental pancreatitis.[39] Likewise, obstruction alone, without pancreatic stimulation, does not cause pancreatitis in the experimental animal. Heavy eating, especially diets high in fat, and excessive alcohol intake, are stimulants to pancreatic secretion that are seen commonly in association with clinical pancreatitis.[16] Secretin, the hormone of the pancreas and drugs producing vagal stimulation are often used experimentally to produce pancreatic stimulation in the presence of pancreatic duct obstruction.[67]

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Toxic Agents Affecting the Parenchyma of the Gland.—This category covers a wide variety of agents which are capable of inducing parenchymal damage to the pancreas. Mumps virus and heavy metal poisoning are rare causes of pancreatitis.[70] Bacteria and bacterial toxins appear to be secondary factors appearing late in the course of the disease, after initial damage of the pancreas has occurred, although theories[21,27] have been advanced implicating bacteria as a primary factor. The substance which is most commonly believed to initiate the inflammatory reaction in the pancreatic parenchyma is the pancreatic juice itself, when it escapes from the duct system. The influence of bile as a noxious substance, initiating inflammation by reflux from the biliary duct system into the pancreatic duct system, remains a debatable issue. The time-honored common channel theory[47] holds that the regurgitant effect of bile plays a primary and important role. However, several observers[16,18,53,81] now feel that an obstructing factor in addition to a common channel with reflux of bile is necessary to cause pancreatitis. In this regard, comment should be made concerning studies on the pressure within the common bile and pancreatic ducts under various conditions. Attempts to measure pancreatic and bile duct pressures have indicated that pancreatic duct pressure is higher than bile duct pressure during all phases of digestion, except occasionally for a brief period as the gall bladder empties.[48] The normal pressure within the human common bile duct is 50 to 150 mm. of water, and it has been shown that a spastic sphincter of Oddi may resist pressures up to 600 mm. of water. According to Doubilet and Mulholland,[18] common duct pressure above 150 mm. of water indicates a spastic sphincter and they believe that this is the most common obstructing factor in chronic relapsing pancreatitis. They are of the opinion that reflux of bile into the pancreas occurs when there is sphincter spasm.

The clinical observation that approximately 50 per cent of patients with pancreatitis have associated cholecystitis and cholelithiasis[44,50] has raised the question of the etiological relationship between these two diseases. This relationship still awaits definition.

Trauma.—Accidental or surgical trauma to the pancreas may infrequently[53] result in localized damage to the duct system with extravasation of enzymes, localized pancreatitis, and at times formation of pseudocysts. When healing occurs, scarring and obstruction of the duct may lead to further attacks of pancreatitis.

Vascular Factors Involved in Pancreatitis.—As will be discussed later under pathology, hemorrhage and necrosis in the pancreas denote the most severe form of the disease. Recent experimental studies in animals[14] suggest that when interference with the blood supply to the pancreas alone is produced, focal necrosis results. When the pancreatic duct is obstructed and the pancreas is stimulated, edematous pancreatitis, not hemorrhagic necrosis, results. However, when the combination of duct obstruction, pancreatic stimulation, and interference with blood supply occurs, diffuse hemorrhagic necrosis of the gland results. These studies suggest that initially all cases of pancreatitis begin as the edematous variety, and in some a secondary impairment of blood supply may result secondary to an inflammatory thrombosis of vessels. In further support

of this thesis is the fact that a small amount of trypsin has the potential capacity of inducing thrombosis in vessels.[66] Post-mortem studies on patients who died of hemorrhagic necrosis of the pancreas, however, have failed to establish the presence of a definitive vascular lesion.[70] This does not, however, rule out the possibility of such a lesion, the evidence for which may have been destroyed during the course of the disease.

PATHOLOGY OF CHRONIC PANCREATITIS

The chief lesion noted in the pancreas in chronic relapsing pancreatitis is scarring of the gland.[16] There are usually varying degrees of atrophy of the epithelial components. Scarring produces obstruction of the ducts which may lead to dilatation of some ducts with formation of cystic areas. Early in the disease the organ is larger than normal, but as repeated attacks occur it may become small and fibrotic. Calcification is a feature which may develop in approximately 50 per cent of cases. This calcification may be present in large or small ducts or in the parenchyma at sites of previous fat necrosis. In some cases scarring may be so extensive that the islands of Langerhans may be reduced in number and size. Cellular exudate consists only of small numbers of round and plasma cells.

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CLINICAL FEATURES OF CHRONIC PANCREATITIS

Symptoms and Signs.—The symptoms of chronic relapsing pancreatitis may be listed as follows: (1) abdominal pain, (2) nausea and vomiting, (3) diarrhea, steatorrhea, creatorrhea, (4) constipation, (5) weight loss (6) jaundice, (7) diabetes mellitus, (8) abdominal mass, and (9) hemetemesis or melena.

Abdominal pain is the outstanding symptom. Characteristically, the pain is epigastric in location with radiation into either upper abdominal quadrant and often to the back. It is usually severe in intensity, with a gradual onset, often precipitated by a bout of heavy eating or alcoholic intake. The pain may last for 24 to 72 hours and often requires narcotics for relief. Frequency of attacks varies, and in some cases the disease will advance to an almost continuous state of pain. Nausea and vomiting often accompany the attacks of pain and probably are reflex in nature.

In late stages of the disease there may occur a retention type of vomiting, due to chronic duodenal obstruction. Diarrhea, with stools often greasy, bulky, and foul smelling, is a common symptom, occurring in approximately one-half of patients.[71] This steatorrhea may occur in bouts, usually following an attack of pain, but in far-advanced cases may become persistent. Some patients complain of constipation, probably caused by limited intake of food or use of narcotics. In some constipation may alternate with bouts of diarrhea.

Weight loss is a common complaint of patients with recurring attacks of pancreatitis. This may be profound, from 25 to 50 pounds during the course of illness, and is due to diminished calorie intake and the digestive disturbance secondary to deficiency of external pancreatic secretion. The incidence of jaundice in relapsing pancreatitis is about 25 per cent.[16] The jaundice may be

due to associated disease in the biliary tract (stone in common bile duct), pericholangitis, or constriction of the pancreatic portion of the common bile duct secondary to inflammation and edema in the head of the pancreas.[10]

Symptoms of diabetes mellitus may be present, since this complication occurs in about one-third of patients with relapsing pancreatitis.[16] In rare instances patients with the disease may develop gastrointestinal hemorrhage with either vomiting of blood or tarry stools. The site of bleeding in these cases is apparently the duodenum, wherein a duodenitis with ulceration occurs. The diminution of external pancreatic secretion may render the duodenal mucosa more liable to acid peptic digestion. Anlyan[2] has found that a duodenal ulcer occurs in all dogs which develop chronic pancreatitis following occlusion of the pancreatic ducts by injection of Vinylite plastic (VYHH-1).

Physical Signs.—Between attacks, physical signs may be minimal, the outstanding signs being evidence of malnutrition and weight loss. During an acute episode, signs may vary from mild epigastric tenderness to more pronounced signs of intra-abdominal infection, with associated hypotension, depending on the severity of the attack. In cases with the complication of pseudocyst, an abdominal mass may be palpable.

X-ray Findings.—One of the common and most helpful findings in patients with chronic pancreatitis is the presence of calcification of the pancreas seen on plain x-ray of the abdomen. This is said to occur in 50 per cent of patients with the disease.[70] Other indirect radiologic findings may be widening or distortion of the duodenal loop due to changes in the head of the pancreas. If the pancreas contains cysts, displacement of the stomach may be noted. On barium study of the small bowel, the findings are usually normal, in contradistinction to the findings in other causes of steatorrhea, such as sprue. Intravenous cholangiography may prove to be of value in demonstrating narrowing of the pancreatic portion of the common bile duct secondary to pancreatitis. Splenoportography may be used to demonstrate cysts of the pancreas seen as a complication in some patients with relapsing pancreatitis.[10]

Complications.—The most outstanding complication of relapsing pancreatitis is severe intractable pain. Since narcotics are commonly used to control it, dependence on these drugs is a relatively frequent occurrence. Diabetes mellitus, jaundice, duodenal obstruction, severe malnutrition, and gastrointestinal hemorrhage have already been mentioned. Five to ten per cent of patients with relapsing pancreatitis develop a pseudocyst which requires treatment.[25] Pancreatic absess, not uncommon following acute pancreatic necrosis, is rare in chronic relapsing pancreatitis. Carcinoma of the pancreas secondary to chronic pancreatitis is uncommon, but may occur. I have seen two such cases.

Laboratory Features.—A variety of tests for diagnosis of chronic disease of the pancreas has been described, and to some extent evaluated. Most of these tests do not differentiate between benign and malignant disease of the organ. Many of them are based on derangements of pancreatic function, and this organ, like the liver, has a large reserve functional capacity. Laboratory studies that may be helpful are: (1) blood enzyme studies, (2) serum alkaline phosphatase determination, (3) studies on blood coagulability, (4) tests to detect impaired

carbohydrate metabolism, (5) stool examination, (6) examination of duodenal contents, and (7) tests of digestive efficiency.

1. Blood enzyme studies: Estimation of serum amylase is the most widely used and the single most valuable test in diagnosis of acute pancreatitis.[10] Unfortunately this is not the case in the chronic relapsing form.[63] Recently, studies have been reported[52,61,80] on serum pancreatic enzymes before and after the administration of a pancreatic stimulant such as secretin or a vagal stimulating drug. It has been stated that secretin alone would not produce a rise in serum amylase in a healthy individual but when combined with morphine or one of the vagal stimulating drugs, such as prostigmine, methacholine (Mecholyl) or bethanecol chloride (Urecholine), a significant rise in serum amylase would occur in a variable number of healthy individuals.[46,52] Morphine and vagus-stimulating drugs supposedly produce an obstructive mechanism in the pancreatic ducts or at the ampulla of Vater.[49]

Wirts and Snape[80] have reported that Urecholine alone produced significant elevation of serum amylase in a majority (no figure cited) of healthy individuals, whereas approximately one-half of patients with chronic pancreatitis or pancreatic carcinoma showed no rise.

On the other hand, Sanchez-Ubeda and Rousselot[61] have reported that the serum amylase was significantly elevated in only one of 31 patients without chronic pancreatitis given secretin and Mecholyl, whereas 5 of 7 patients with chronic pancreatic disease showed a significant elevation.

Thus, there are two lines of approach to the development of a pancreatic function test based on serum enzyme changes after pancreatic stimulation. One approach presumes a significant rise in enzymes after stimulation in a high percentage of normal persons, but no rise in patients with pancreatic disease; while the other presumes no rise in normal patients but a significant elevation in a majority of patients with pancreatic disease.

In a study of my own,[63] serum amylase determinations have been made in a group of control patients and patients with chronic pancreatic disease before and after intravenous secretin (Lilly, 1.5 units per kilogram), and after secretin and Urecholine (0.05 mg. per kilogram) given subcutaneously. Two significant elevations in serum amylase were found after secretin in 32 control patients and in one of 11 patients with chronic pancreatitis. No significant change in serum amylase occurred after secretin and Urecholine injection in another group of 14 control patients, nor in 6 patients with chronic pancreatitis. In this study, serum amylase determination after pancreatic stimulation with secretin alone or with secretin and Urecholine did not yield information of diagnostic aid in chronic pancreatic disease.

Serum lipase determination, like serum amylase, may be of aid in diagnosis of acute pancreatitis, but its value in diagnosis of chronic pancreatitis is questionable.

2. Serum alkaline phosphatase determinations: Elevation of serum alkaline phosphatase has been found in dogs after pancreatic duct ligation. Sun[73] has reported a significant rise in serum alkaline phosphatase after secretin stimulation

in some patients with cancer of the pancreas or chronic pancreatitis. The value of this test as an aid in diagnosis of relapsing pancreatitis requires further evaluation.

3. Studies on blood coagulability: The high incidence of widely disseminated venous thrombosis accompanying carcinoma of the pancreas[72] suggested a relationship between pancreatic disease and blood coagulability. The generalized hypercoagulability seen in some patients has been attributed to the release of trypsin into the systemic circulation via the portal circulation secondary to pancreatic duct obstruction.

In studying the relationship between pancreatic secretions and blood coagulation, Turcatti[75] noted a prolongation of the clotting time in 5 of 11 dogs submitted to pancreatectomy and 3 of 4 dogs with pancreatic duct ligation. Ferrari and Cortese,[26] in a similar study, found a slight prolongation of the clotting time of dogs following pancreatic duct ligation and the formation of external pancreatic fistulas. They both concluded that the influence of the pancreas on blood coagulation was via the external pancreatic secretions, and upon removal of these secretions there was a prolongation of the coagulation time. Lasher and McCabe[38] produced acute pancreatitis in dogs with bile and noted a slight shortening of the clotting time and an initial decrease in prothrombin time. Innerfield, Angrist, and Benjamin[31] have measured plasma antithrombin patterns in patients with pancreatic disease and have reported an elevated antithrombin titer in acute pancreatitis, exacerbations of chronic relapsing pancreatitis, pancreatic cysts, carcinoma of the head of the pancreas, and fibrocystic disease of the pancreas. Rush and Cliffton[60] have reported an increased titer of serum proteolytic activity in dogs with experimental acute pancreatitis.

Using a sensitized clotting test with an anticoagulant, sodium polyanhydromannuronic acid (Paratol C), I have demonstrated[63] a measurable increase in the clotting reaction of blood in 6 of 8 patients with chronic pancreatitis. These results have been confirmed by Moser.[45]

4. Tests to detect impaired carbohydrate metabolism: Mention has already been made of the fact that approximately one-third of patients with chronic relapsing pancreatitis develop diabetes mellitus. Before this disease process becomes fully established, patients may develop hyperglycemia and glycosuria during an exacerbation of their disease process. Measurement of blood and urinary sugar, and a glucose tolerance test, therefore, should be routinely applied to all patients suspected of having chronic pancreatitis.

5. Studies on the stool: Gross inspection of the stool in a patient who develops steatorrhea as a complication of chronic pancreatitis reveals it to be bulky, light in color, greasy and with the tendency to float on water. Microscopic examination of the stool may reveal excessive numbers of fat droplets, recognizable by staining with sudan III. Chemical analysis of fat content of the stool is cumbersome and not generally adaptable for routine clinical use. The stool may be further tested for the presence of tryptic activity by placing a specimen on an x-ray film, which serves as a substrate for gross estimation of tryptic activity.

6. Examination of duodenal contents: The evaluation of pancreatic function in health and disease by measurement of enzymes in duodenal juice before and

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after a pancreatic stimulant dates back to 1939, when Lagerlof[37] and his group in Sweden first employed and described the procedure. The method utilized secretin as a stimulus, and samples of the duodenal juice were obtained for analysis through an indwelling gastroduodenal tube. The original analysis included estimation of the volume of secretion, bicarbonate content, and the pancreatic enzymes amylase, trypsin, and lipase. These studies revealed a wide variation in normal values, but significantly low values in cases of proved pancreatic disease. Since these original studies, the test has been modified in various ways and several reports have appeared in the literature, all of which tend to confirm the impression that the test is of value in estimating pancreatic function and as an aid in the diagnosis of chronic disease of the pancreas. The test as originally described and usually done is admittedly time consuming, somewhat uncomfortable to the patient, and may fail to show early derangement in pancreatic function. Reports concerning enzyme analysis in the duodenal juice after pancreatic stimulation have not been uniform, thus making comparison of results difficult to interpret. There is some disagreement concerning the length and manner of collection of the sample for analysis, the type and amount of pancreatic stimulant used, and the relative importance of the various analyses carried out. Space does not permit a review of these various concepts. Dreiling,[22] who has carried out the most extensive study on the variable factors in the test, is of the opinion that an 80-minute sample should be collected after the injection of secretin, and that there is less variation in control values if volume and enzyme content of the duodenal juice are corrected in regard to the kilogram weight of the patient tested. Since criteria for normal and abnormal values are not uniform due to variance in technique, it is probably necessary that control values be established in each laboratory using the test. It is of interest that a tabulation of a series of reports[7,17,19,37,51,63] on use of the secretin test disclosed that, using each author's own classification of normality, the test was abnormal in 72 of 86 cases of chronic pancreatitis (83 per cent accuracy).

7. *Tests of digestive efficiency:* Since the pancreas is one of the most important sources of digestive enzymes in the intestinal tract, one might expect disease in this organ to lead to impaired digestion. Several tests have been developed with this supposition as their basis. A gelatin tolerance test has been described, in which amino-acido-nitrogen values are determined before and at intervals after the ingestion of gelatin. Although abnormal values have been found in children with cystic fibrosis of the pancreas,[79] the test has not proved reliable for pancreatic function in adults.[1] Protein digestion may be further evaluated by the use of an I^{131}-labeled albumin by mouth and measurement of the isotope in the blood, urine, and feces. Using this technique, I found an abnormally low content of blood radioactivity in 9 of 10 patients with proved pancreatic disease, when compared to normal controls.[68]

A starch tolerance test has been described by Althausen and Uyeyama[1] wherein a glucose and starch tolerance test is done and the results are compared with those in normal controls. Determinations of blood sugar are made preceding and at intervals of three hours after the patient is given a starch suspension. In addition, the patient is given a glucose tolerance test. The re-

sponses to the two tests are compared, and the extent to which the rise in blood sugar after glucose exceeds that after starch is calculated in percentages and compared with the established normal range. Six of 10 patients with chronic pancreatitis were found to have an abnormal test.

Recently I have reported[65] a pancreatic function test based on the administration of a fat meal containing I^{131}-labeled fat and the subsequent measurement of radioactivity in the blood and feces. The technique of the test was as follows:

> Patients were fasted from 12 midnight to 9 A.M., when they were given 0.9 c.c. of Lugol's solution orally, followed by a test meal consisting of 50 mc. of I^{131}-labeled glycerol trioleate, 0.5 c.c. of peanut oil per kilogram of body weight, emulsified in an equal amount of water, and 2 to 3 c.c. of Tween 80. Twenty grams of barium sulfate was added to the test meal and the ingredients mixed in a Waring Blendor. Following ingestion of the meal, the beaker was rinsed twice with 50 c.c. of water and the subject drank the rinse, but otherwise fasted throughout the test. The beaker was then assayed for residual radioisotope content, and this was taken into consideration in the final analysis. All subjects were ambulatory during the test.
>
> Two cubic centimeters of venous blood was withdrawn at 4, 5, and 6 hours following the test meal. Each sample was placed in a separate tube and assayed for radioactive I^{131} content in a calibrated, sodium iodide, thallium activated, scintillation crystal well counter. The total blood volume was assumed to be 7.2 per cent of body weight. Using the measured radioactivity of the 2 c.c. sample and the calculated total blood volume, the total radioactive I^{131} blood level was determined and expressed as a percentage of the ingested material. All stools passed during the next 48 hours were collected in individual containers. The containers used were plastic-lined, 1 pint, waterproof cartons. Care was taken to keep the samples free of urine. A sodium iodide, thallium activated, scintillation crystal detector and a Nuclear Instrument and Chemical Corp. Model 161-A scaler were used in checking all stool samples for radioiodine content. The detector was positioned 15 cm. from the top surface of the sample container. All samples were counted for sufficient time to give statistical accuracy to the data. A 100 Gm. homogeneously distributed standard solution containing an amount of I^{131} equivalent to that ingested by the patient—allowing for decay—was counted in the same manner. Direct comparison between the net sample counts per minute and the net standard counts per minute allowed a total radioiodine recovery in the feces to be determined as a percentage of the ingested material.

Control levels of blood and fecal radioactivity with the use of this technique were established on 25 volunteers.[8,62]

The test yielded information of diagnostic value in 10 of 12 patients found to have chronic relapsing pancreatitis, and in 17 of 18 patients with pancreatic carcinoma. In the absence of disease of the small bowel, pyloric obstruction, or gastric surgery, an impairment of fat absorption using this technique is strongly suggestive of pancreatic disease. The method can further be used as a laboratory aid in evaluating substitution therapy in patients with pancreatic insufficiency. It does not, however, distinguish between benign and malignant disease of the pancreas.

TREATMENT OF CHRONIC PANCREATITIS

One of the most controversial aspects of recurrent pancreatitis is the problem of management. Although much can be accomplished by medical management of certain complications (diabetes, malnutrition), most clinicians agree that management is primarily a surgical problem. A wide variety of surgical approaches has been advocated, which attests to the fact that no single method has proved satisfactory in all cases.

The surgical procedures that have been employed may be classed as follows: (1) operations on the biliary tract, (2) procedures designed to decrease pancreatic secretion, (3) operations on the pancreas, and (4) operations on autonomic nerves to relieve pain.

Operations on the Biliary Tract.—Evidence now suggests that patients who have associated biliary tract disease and chronic pancreatitis are greatly benefited by operative correction of their biliary tract disease,[53,81] which most often is chronic cholelithiasis. Many patients will have no further attacks of pancreatitis after removal of the diseased gall bladder and stones in the common bile duct, if present.[6] This is the most favorable group of patients to treat, since subsequent procedures on the pancreas will probably be unnecessary. On the other hand, when there is no disease in the biliary tract, removal of the gall bladder and/or drainage of the common bile duct is of questionable value in prevention of further attacks of pancreatitis. Priestley[53] has reported that only 13 of 33 patients were relieved by prolonged external drainage of the common bile duct. Internal biliary drainage by cholecystenterostomy has been employed with limited success.[53] Bowers[15] has reported good results in 15 of 16 patients with relapsing pancreatitis in whom he transplanted the common bile duct into the jejunum. Most surgeons, however, are reluctant to transect the common duct for benign disease.

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For the purpose of discussion, operations on the sphincter of Oddi are included under operations on the biliary tract. These procedures include dilatation of the sphincter and actual cutting of the sphincter via the common bile duct or duodenum. This operative procedure is based on the theory that due to either fibrosis or spasm of the sphincter of Oddi there is partial obstruction of the biliary and pancreatic ducts; and because a common channel exists at the ampulla of Vater, reflux of bile into the pancreatic duct occurs, which leads to pancreatitis. Doubilet and Mulholland[18] have been the chief advocates of sphincterotomy in chronic pancreatitis and have recently reported results in 319 patients so treated. They found a common channel in 316 of the 319 patients. Results of the operation were good in 169 of 190 patients who had been observed two years or longer following sphincterotomy. Most of the failures occurred in those continuing an intake of alcohol. They advise that cholecystectomy always be done with sphincterotomy and that patients be kept on a fat-free diet.

Procedures Designed to Decrease Pancreatic Secretion.—Operative procedures of this type include vagotomy with gastroenterostomy and subtotal gastrectomy. These procedures have been employed infrequently. McCleary[42] reported favorable short-term follow-up results in a group of patients following vagotomy with gastroenterostomy, but a long-term follow-up study has not yet been reported. Failure of vagotomy to relieve attacks of pancreatitis has also been reported.[54] Subtotal gastrectomy has been employed in a few patients with both favorable[59] and unfavorable results.[33]

Operations on the Pancreas.—Direct operations on the pancreas have increased in frequency during the past few years. Removal of calculi from the main pancreatic duct has been reported by several authors.[24,41,53] Resection of the pancreas, either partial or total,[16] has been reported. Cattell and Warren[16]

feel that they have obtained their best results with partial pancreatectomy. They report that 8 of 11 patients with far-advanced disease were relieved by pancreatoduodenectomy, leaving the tail of the gland, and 6 of 7 patients were relieved by distal pancreatectomy. These authors feel that total pancreatectomy is an unwarranted procedure except in occasional cases when other less radical procedures have failed. It is an operative procedure of considerable magnitude and leaves the patient a permanent diabetic.

Another direct operative approach on the pancreas has been introduced by DuVal.[23] The main duct in the tail of the pancreas is cannulated and a pancreaticogram obtained. If the main duct is dilated and an obstruction found in the head of the pancreas, a caudal pancreaticojejunostomy is performed, using a Roux-en-Y type of anastomosis. The results of this procedure remain to be evaluated.

In patients who develop a pseudocyst as a complication, an operative procedure for drainage of the cyst is usually indicated. The procedures employed are either internal or external drainage of the cyst, or rarely its excision. Cattell and Warren[16] have reported excision of the cyst combined with partial pancreatectomy. In the past, external drainage, by marsupialization, was the most commonly used procedure. This procedure is often associated with a long-standing pancreatic fistula and with frequent recurrence of the pseudocyst.[16] Recently the anastomosis of the cyst to some portion of the intestinal tract has yielded very satisfactory early results.[69]

Operations on Autonomic Nerves to Relieve Pain.—Many reports have appeared in the literature advocating various types of operative procedures for relief of pain in relapsing pancreatitis. Unilateral[40] and bilateral splanchnicectomy,[56] splanchnicectomy combined with vagotomy,[57] and celiac ganglionectomy[28] have been advised. Ray[55] has shown that pain fibers from the pancreas pass through the celiac ganglion and thence principally through the greater splanchnic nerves. Although early results after these operative procedures appear good, there are no reports in the literature, according to Priestley, in which patients have been evaluated five years following the procedure. Several authors have commented on the temporary relief afforded by these operative procedures on the sympathetic nervous system.[16,53] If a procedure of this type is selected, celiac ganglionectomy appears to be the procedure of choice, since, theoretically, it would achieve the following:

1. Remove the neurogenic stimulus to pancreatic secretion by interruption of vagal secretory fibers traversing the celiac ganglion.
2. Prevent or relieve neurogenic spasm of the sphincter mechanism at the ampulla of Vater.
3. Relieve pain of pancreatic origin by interruption of visceral pain pathways traversing the celiac ganglion and plexus.
4. Improve pancreatic blood flow by sympathetic denervation of blood vessels.
5. Allow adequate chance for exploration to ensure correct diagnosis.

There is, therefore, a variety of operative procedures available for the treatment of patients with chronic relapsing pancreatitis, and the operative

procedure should be chosen which best fits the need of each individual case. In patients who have associated biliary tract disease, this should be corrected as the primary procedure, and this procedure alone affords relief in many patients. For those who do then develop recurring attacks, and for those who have no associated biliary tract disease, several operative procedures are available which have given satisfactory results in a majority of patients. Multiple procedures may be necessary in intractable cases.

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Book Reviews

THERAPY OF FUNGUS DISEASES—AN INTERNATIONAL SYMPOSIUM. Edited by Thomas H. Sternberg, M.D., and Victor D. Newcomer, M.D. Pp. 337, with 42, figures; indexed. Boston, 1956, Little, Brown & Company. Price $7.50.

This volume represents papers presented at a two and one-half day symposium on fungus diseases occurring in this and eight foreign countries. The conference was sponsored by the Division of Dermatology of the School of Medicine and the Extension Divisions of the Medical School of the University of California at Los Angeles, and made possible by the financial assistance of the Squibb Institute for Medical Research. The symposium covered much more than therapy. In fact, the data on successful therapeutic procedures and drugs for the treatment of both superficial and deep mycotic infections were rather meager and forcefully emphasized the validity of the statement by Dr. Pillsbury in his introductory remarks, "Among all the microbial infections of man, the diseases caused by fungi are perhaps the most difficult to modify in their course or to prevent." The prevalence of the dermatoses and systemic fungal infections are given for India, France, Argentina, Brazil, Mexico, the Philippines, the Ukraine and Italy, together with experience in treatment. Other chapters deal with the ecology of fungi and the epidemiology, pathogenesis, pathology, and immunologic aspects of their respective diseases. Dr. Waksman discusses the origin, chemical nature, and activity of antibacterial and antifungal antibiotics derived from bacteria, fungi, and actinomycetes.

Considerable space is devoted to the pharmacology, fungistatic and fungicidal activity of Mycostatin (Squibb) in the treatment of experimental infections in animals caused by *Monilia*, *Coccidioides immitis*, *H. capsulatum*, and *Blastomyces*. Experience in the treatment of human infections caused by these agents as well as superficial fungi is also recorded. Encouraging experiences with other antifungal drugs and antibiotics in the treatment of experimental infections are recorded. Those deserving further clinical trial include MRD-112 (Merrell), 2-hydroxystilbamidine (Merrell), antibiotic 1968 (Nepera), nitrostyrenes, filipin, an antibiotic, and rhodanine, an organic sulfur compound.

This volume will be of value of anyone interested in the fungi and the diseases they cause. The investigator will appreciate the remarks of Dr. Pillsbury that "approaches to the therapy of fungus diseases must be increasingly bold and imaginative and necessarily will involve basic studies which do not—indeed should not—have any prospect of immediate practical application." He then sets forth "approaches which appear worth while."

Clayton G. Loosli

CIBA FOUNDATION SYMPOSIUM ON PAPER ELECTROPHORESIS. G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Elaine C. P. Millar, A.H.-W.C., A.R.I.C. Pp. 224, with 74 illustrations; indexed. Boston, 1956, Little, Brown and Company. Price $6.75.

In the preface to this volume one finds an explanation that the symposium was fitted into a previously planned schedule by the Ciba Foundation for the dual purposes of clarifying the technique of paper electrophoresis and of helping the overseas participants to attend another Congress which was held immediately afterward. This reviewer applauds the editors for their

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forthright honesty in explaining the very apparent lack of planning of a well-rounded program, and he hopes that the participants enjoyed the other Congress mentioned so that at least part of the expressed purpose was realized.

A number of fine points concerning technique are made by the notable contributors, but most of these points are well hidden in the discussions. A number of methods are discussed but with insufficient detail to aid the beginner and lacking in newness to intrigue those who have worked in the field. Clinical detail is clearly not part of the symposium. The whole sense of the meeting seemed admirably stated by one discussant of a paper concerning the reading of the electrophoretic strip: "I think I could sum up this discussion in the following way: that it really is not possible to recommend one procedure or the other; it must vary from case to case and the research worker has simply to use his common sense." If his common sense tells him not to buy this book, the research worker will save $6.75.

Ernest W. Smith

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CIBA FOUNDATION SYMPOSIUM ON BONE STRUCTURE AND METABOLISM. G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. Pp. 299, with 121 illustrations; indexed. Boston, 1956, Little, Brown and Company. Price $8.00.

This book is published by the Ciba Foundation, which was founded for the promotion of international cooperation in medical and chemical research. Its appearance at this time is much appreciated by those who are working in the field of bone structure and metabolism. It reports the progress made in this field up to the time of the conference, which took place in July, 1955. The participants were well selected and represent leaders in the field. Not all of those who have contributed heavily to this field were present at the conference, but the authors usually presented their own work in such a way that reference to the work of those who were absent was noted. The bibliographies at the end of each chapter are not exhaustive but they appear adequate.

Several disciplines are represented: anatomy, biochemistry and chemistry, physics and biophysics, and clinical medicine. The conferences were conducted in a manner similar to those sponsored by the Josiah Macy, Jr., Foundation on Metabolic Interrelations which were held in New York yearly between 1949 and 1953. A subject was presented by an authority in each of the fields of research represented at the conference, and subsequently an open discussion was held by any of the participants who cared to comment on the work presented. These discussions are reported at the end of each chapter. In this way, the multiple disciplines represented at the conference were brought to bear on each of the subjects. These discussions are printed and increase the value of the material formally presented in each chapter.

More European participants were able to attend this conference on bone than those which were previously held in New York by the Josiah Macy, Jr., Foundation, and points of view which did not appear in the Transactions of the Conferences on Metabolic Interrelations are therefore present in this Ciba Foundation Symposium. This symposium report brings one up to date on research progress in the field of bone structure and metabolism as well as any book could do. The material is put together simply and the illustrations are valuable. It is the opinion of the reviewer that anyone working in the field of bone structure and metabolism, including internists who are interested in the problems of electrolyte balance, and orthopedic surgeons who are interested in bone as a skeletal structure, should read this book.

Robert A. Robinson

ALCOHOLISM AS A MEDICAL PROBLEM. Edited by H. D. Kruse, M.D., New York, 1956, Hoeber-Harper. Pp. 102; indexed. $3.00.

This small volume consists of a series of articles on alcoholism by several contributors who participated in a conference held under the auspices of the Committee on Public Health of the New York Academy of Medicine and the New York State Mental Health Commission. The

purpose of this conference was as follows: "To introduce the problems of alcoholism to the physician; to create in him an appreciation of the magnitude of the disease. . .; to direct his attention to his new responsibility to the alcoholic and to encourage him to assume it; to acquaint him with basic medical facts and principles about alcoholism; and to stimulate research on the causes of this disease, and on the care and treatment of the patient." To some extent, these purposes have been fulfilled, but practicing physicians who daily have to cope with alcoholics will find little that will tell them what to do or even help them evaluate what they are doing already. In addition, the serious problem of physicians' negative attitudes toward alcoholics, in the main consisting of the tendency to consider them as generally undesirable, and the implications of this for research as well as treatment, are given inadequate attention. Much of the specific information that is offered is a reiteration of common knowledge. However, certain refreshing viewpoints are presented, particularly those concerning the application of epidemiologic principles to alcoholism and those attempting to determine whether alcoholism is or is not a disease.

The book will be of value to those participating in research endeavors pertaining to alcoholism for it provides some perspective from which to view the entire field. Otherwise, its use will be limited.

Lester H. Gliedman

DISEASES OF THE LIVER. Edited by Leon Schiff, M.D., Ph.D. With a foreword by Cecil J. Watson, M.D., Ph.D. Pp. 738, with 244 illustrations; indexed. Philadelphia, 1956, J. B. Lippincott Company. Price $16.00.

One should welcome the opportunity of saving a great deal of time while enjoying a lengthy textbook. This unusual circumstance is made possible with this volume. Dr. Schiff and his contributing authors have so well illuminated the mechansims of the various disorders of the liver that the need for the time-consuming and usually feckless method of rote learning is obviated.

A reorientation of the classification of disorders of the liver to conform to etiology rather than morphology has been progressing for some time, the progress being recorded in progressively lucid textbooks. Now it would seem that the authors of some of those textbooks, together with many other recognized experts in the field, have taken vorpel blades in hand and have administered the *coup de grace* to the obfuscation which has continued to perch on the corpse of purely descriptive morphology.

In the early chapters the functional unit of the liver is described in terms of cellular anatomy and enzymatic content, which are in turn related to clinical problems. As an example, one might use the explanation which is given of glycogen storage disease in terms of the deficiency of glucose-6-phosphatases, an account which elucidates the clinical features of the disorder. Accumulated data concerning the normal and pathologic responses of the liver are presented with a wealth of documentation for the exposition of each function. Dr. Hartroft's sixteen pages concerned with the production of experimental hepatic damage are all too short, but bespeak a tremendous amount of worth while effort by many workers in the field. A perusal of the brief section on the liver function tests should be worth while for anyone who orders these from the laboratory.

In the remaining seventeen sections, the etiologic factors responsible for hepatic disorders are considered. Viral hepatitis is discussed in considerable detail from a pathologic and clinical point of view. The ubiquity of this disorder and the frequency with which it is blamed for acute and chronic liver destruction make this review particularly worth while. In the chapters on Toxic Hepatitis, and Hepatitis Associated with Systemic Infections, Dr. Klatskin has compiled and discussed an extensive list of hepatotoxic agents and mechanisms. The sections on cirrhosis which follow delineate portal cirrhosis (Laennec's cirrhosis) from postnecrotic cirrhosis from an etiologic standpoint, while it becomes clear to the reader that the end point for each may be morphologically indistinguishable. Dr. Kunkle's section on biliary cirrhosis very nicely presents the picture of biliary obstruction, either intrahepatic or extrahepatic, and of a wide variety of causes as a unit. It is my belief that the concepts of pathogenesis which are embodied within these chapters on cirrhoses are poorly understood by most casual students of the liver and, thus, should be particularly profitable reading for many.

The sections concerned with hemachromatosis and with hepatolenticular degeneration of Wilson are concise gems of achievement. Here are two illustrations of previously obscure metabolic disorders which have yielded most of their secrets, and which should be entertaining reading for all. Tumors, abscesses, and biliary tree are well summarized and maintain the essential good features of the book to the very end.

For those who don't really read but who do like the solid feel of a Cadillac door, the shutter action of a good camera, or a good book, this volume is well printed on good paper and is handsomely and well bound.

Ernest W. Smith

OBSERVATIONS ON KREBIOZEN IN THE MANAGEMENT OF CANCER. By A. C. Ivy, Ph.D., M.D., John F. Pick, M.D., and W. F. P. Phillips, M.D. Pp. 88, with 9 tables and 8 figures. Chicago, 1956, Henry Regnery Company. Price $2.50.

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This is a disturbing book from beginning to end. The reader is immediately confronted with a list of errata which would be considered excessive for a book twice the size of this one. The word "palliative" is defined once and then the definition footnoted four more times. The authors state that there is considerable evidence that the body contains a substance capable of counteracting cancerous growth (which may well be true) but then go on to equate this substance automatically with "Krebiozen" (which is likely not to be true). It is hard to suppress a queasy feeling about Krebiozen when the minute dosages employed are discussed; while it is true that substances are available in nutrition and pharmacology which are active in man in dosages of a few gamma, such compounds are extraordinarily rare.

One cannot agree with the authors that their investigations have ruled out a placebo effect as an explanation for much of their "success." Dr. Ivy and his colleagues rely exclusively on the fact that patients who do not know they are getting "Krebiozen" do as well as those who know that what they are getting is "Krebiozen." How this is to prevent patient enthusiasm for therapy in general is not explained.

The authors try to make use of the fact that there is a correlation between length of life and number of Krebiozen injections. They are apparently aware that anyone happening to live longer for any reason would by definition have more opportunity for repeated injections, but in a curious demonstration of Alice-in-Wonderland reasoning the authors use these data to prove that "one can not expect 2 or 4 doses of a remedy . . . to produce a . . . 'four or five year cure' of . . . patients whose life expectancy is only 1 to 6 weeks."

In view of the almost completely negative report of the Council on Pharmacy and Chemistry (see *J. A. M. A.* 147:864, 1951), what can one say about the results of Ivy and his associates? An easy out would be to call the proponents of Krebiozen frauds. A more generous and probably more correct explanation is to credit their enthusiasm to a combination of good intentions and lack of appreciation of the natural history of cancer. The Council report referred to above implies that: (1) Doctors are well aware that cancer is not "an invariably rapid and lethal illness." (2) A shrinkage or disappearance of one or several tumor masses in the presence of progressive growth of other tumor masses in the same individual is not convincing evidence of anti-tumor effect. (3) "Subjective improvement [in patients with cancer] is the most misleading and undependable single observation" in this field. Without taking issue with the truth of these statements, one wonders whether they coincide with the ideas of physicians in general and cancer investigators in particular. Dr. Ivy's report sounds very much like a host of other uncontrolled reports on alleged oncolytic drugs. What are needed badly are some reliable data on the natural life history of various neoplasms and (as Ivy points out) some controlled trials in the area of cancer therapy.

Louis Lasagna